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of the district of columbia

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MEDICAL ANNALS
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SCIENTIFIC ARTICLES

Tc-99m Labeled Red Blood Cells: A New Radiopharmaceutical for the Determination of Total Blood Volume and Blood Pool Scanning. Richard C. Reba, M.D., William C. Eckelman, Ph.D. and Solomon N. Albert, M.D. . . 1

Quantitative Excretion of Senokot in Human Breast Milk. Milton W. Werthmann, Jr., M.D. and Stephen V. Krees, M.S. 4

Spectrum of Bowel Disease Associated with Use of Oral Contraceptives. David A. Morowitz, M.D. and Barry H. Epstein, M.D. 6

Total Body Asanguineous Hypothermic Perfusion and Blood Volume Exchange in Dogs. Juan C. Agostinin, M.D., Asit P. Basu, M.D., Solomon N. Albert, M.D. and Karel B. Absolon, M.D., Ph.D. 11

Intra-Gastric Rupture of a Splenic Artery Aneurysm. Jerry B. Rogers, M.D. and Jerome W. Canter, M.D. . . . 14

Medroxyprogesterone Acetate (Provera[R]) Therapy in Acromegaly Associated with Heart Disease. Howard W. Wallach, M.D., Jay R. Shapiro, M.D. and Sander H. Mendelson, M.D. 17

OTHER FEATURES

The View Box 16

106th President of the Medical Society of the District of Columbia—Irving Burka, M.D. 24

Medico-Legal Report. Liability for for Transfusions of "Bad" Blood 27

New Associate Editor, The Medical Annals of the District of Columbia—Robert B. W. Smith, M.D., F.A.C.P. . . . 31

Book Reviews 37

In A Darkness (Wechsler) Reviewed by Robert E. Moran, Jr., M.D.

Heart Block (Cosby and Bilitch) Reviewed by Joseph Lindsay, Jr., M.D.

Clinical Concepts of Infectious Diseases (Cluff and Johnson) Reviewed by John C. Perkins, M.D.

The First Congress of the International Strabismological Association (Fells) Reviewed by Thomas Frey, M.D.

Drugs and the Public (Zinberg and Robertson) Reviewed by Deanne Knapp, Ph.D. and Arthur Ruskin, M.D.

Congenital Abnormalities in Infancy (Norman) Reviewed by Gordon B. Avery, M.D., Ph.D.

Homeopathy in America (Kaufman) Reviewed by John Stubenbord, M.D.

Textbook of Electrocardiography (Littmann) Reviewed by Antonio C. deLeon, Jr., M.D.

Classified Advertisements 10

Information for Authors 11

Statement of Ownership 11

Index of Advertisers 12

Advertising and Subscription Information 11

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PRESIDENT'S MESSAGE

Phrases From A Pensive President

Irving Burka, M.D.

I begin my term as your president amidst the ferment and turmoil in Medicine. As Charles Dickens said of the French Revolution, so it may be said of Medicine today, "it is the worst time and it is the best time."

As I write this, I cannot help but reflect on our aims and goals. When one thinks of the practice of medicine of not so long ago—a time of relative tranquility, individualism, and simplicity, to the present time of Peer Review, utilization, and HMO, when the term for physician has become provider, and for the patient, consumer—it becomes apparent that our Medical Society has done a great deal in smoothing the path for this transformation.

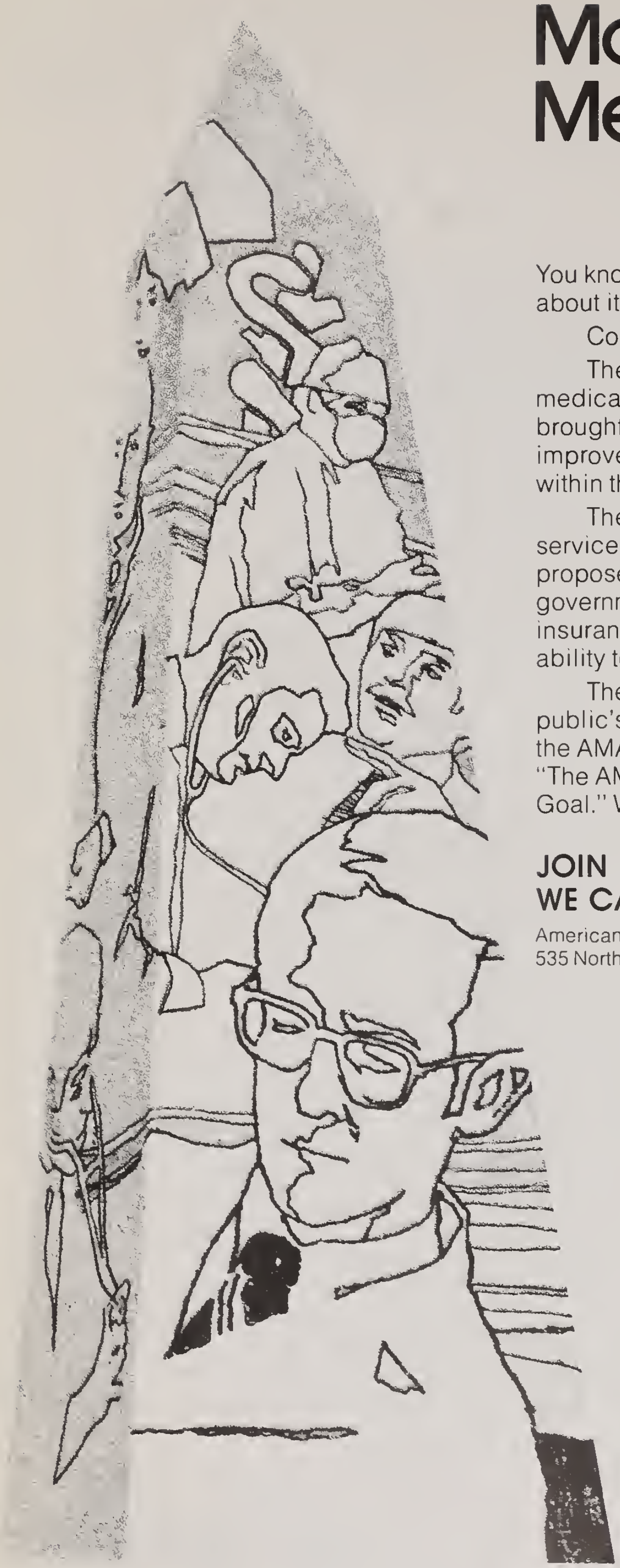
We have always had excellent leadership, both at the top and in our Committee Chairmen, but I must confess that I am most impressed by my immediate two predecessors, who have been most progressive and innovative in their approach to our problems.

In the forseeable future we will be faced with greater stress on Peer Review and Utilization. Let us recognize this; Peer Review is here to stay! This being true, then we have the choice of either permitting third party (government or carrier) agencies to be our monitors, or we lead the way by setting up our own Peer Review foundation, acceptable to and respected by everyone.

The public, which is becoming more sophisticated and knowledgeable, is demanding quality medicine, better distributed, and will insist that the physician, not only be better trained, but that he continue his education throughout his professional career, and give proof of it. If we do not show the way in this field, then certainly recertification and relicensing by government agencies will become a way of life.

Our concern as a profession with the welfare of the community is obvious. We have been and will continue to be activists in promoting all programs, such as, provisions for adequate care for the aged and the disadvantaged throughout the entire area; proper distribution of available medical personnel and facilities; control of guns, air, water and noise pollution, and the fight against the great tragedy of drug addiction and abuse.

Last, but not least, I am most concerned that the "Giant" in organized medicine at times behaves like a Lilliputian. We have great power for good within us, and yet we allow the slings and arrows of unfair and destructive critics to hold us not only accountable for all the ills of the world, but to make us impotent. The story of the American System of Medicine must be told, and its magnificent contribution to the health and welfare of this nation should be emphasized. It has become in this century the standard of excellence for all the world. At the same time, we must make every effort to make it available to all segments of our society at a price it can afford.



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EDITORIALS

On the Subject of Interdependence

In many cities there exist one or more large hospitals which justifiably take pride in offering the highest quality of medical care to the entire community. These non-university "community" institutions and the Washington Hospital Center is one such hospital—have invested a large part of their resources in developing teaching programs designed to attract young physicians who, upon completion of training, will continue to serve the needs of the area. Recently, many of these community teaching institutions have, for mutual support and academic enrichment, affiliated with neighboring university medical centers. These affiliations have at times created some concern and mistrust on the part of both affiliate and university and their staffs. In all parts of the country, many affiliations have lurched backward and forward in a disorganized manner. However, the goal of affiliation is clear—effective utilization of major community resources for the betterment of patient care: this is what medicine is now under public mandate to achieve with minimum delay. There is a recognized common denominator to assist the achievement of quality care by all hospitals and that is medical education—both undergraduate and postgraduate. It is becoming clear that the undergraduate should receive increased exposure to medicine as practiced in the community. On the other hand, the practicing physician should continue to engage in educational activities at an institution well equipped to provide for updating of skills or the acquisition of new skills. The university medical center should be the place where teaching and research create new principles in care and where new stimuli are generated. The community teaching hospital must assume the role of the interphase between the academic center and the practicing physician—the place where patient care gains through ready access to new ideas. This mutual interdependency must be accepted by medical educators, practicing physicians, and institutions alike.

Jay R. Shapiro. M.D.
Director, Medical Education
Washington Hospital Center

Thomas W. Mattingly, M.D.

Well Done, Dr. Thomas W. Mattingly

It is fitting that in this issue of the MEDICAL ANNALS OF THE DISTRICT OF COLUMBIA, which honors one of the foremost teaching institutions and medical centers for patient care in this area, that we take cognizance of one of the men responsible for some of its excellent achievements—Dr. Thomas W. Mattingly. After his retirement in 1958 from the U.S. Army as Chief of the Department of Medicine at Walter Reed Army Center, Dr. Mattingly joined the Washington Hospital Center, first as Director of Medical Education and then as Chief, Department of Medicine from 1962 to 1967. In these capacities, Dr. Mattingly was an inspiring and provocative teacher who brought out the best in interns, residents, staff members and attending physicians.

The numerous accomplishments of this dynamic man are well known to the physicians of this area. A former Governor and now Regent of the American College of Physicians, Dr. Mattingly has always been in the forefront of American medical education. Dr. Mattingly is now retiring and moving to Columbia, South Carolina. Those of us who know him best know that he will continue to inspire and stimulate those with whom he comes into contact, even though less active in the field of medicine.

Raymond Scalettar, M.D.
Editor

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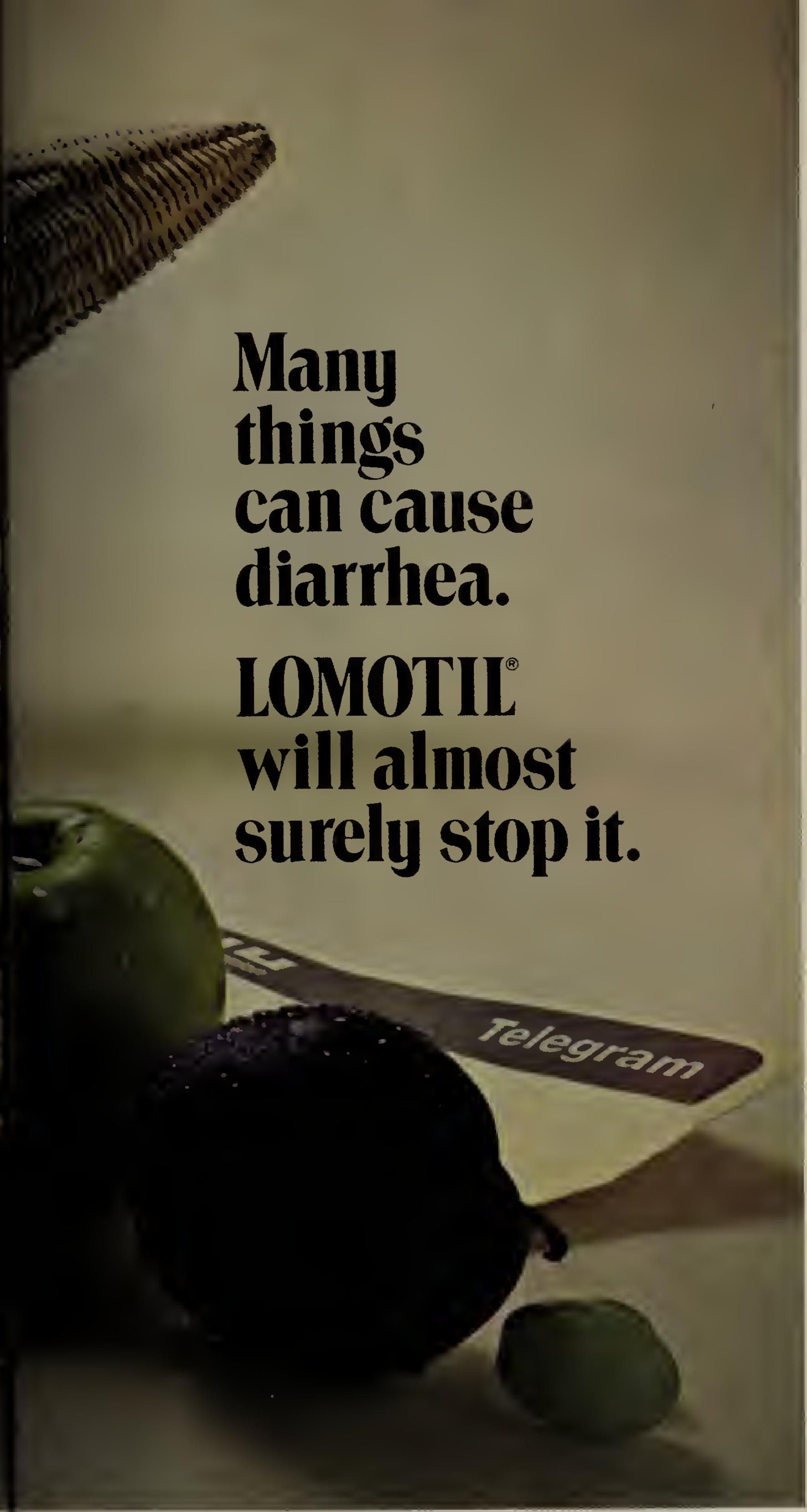
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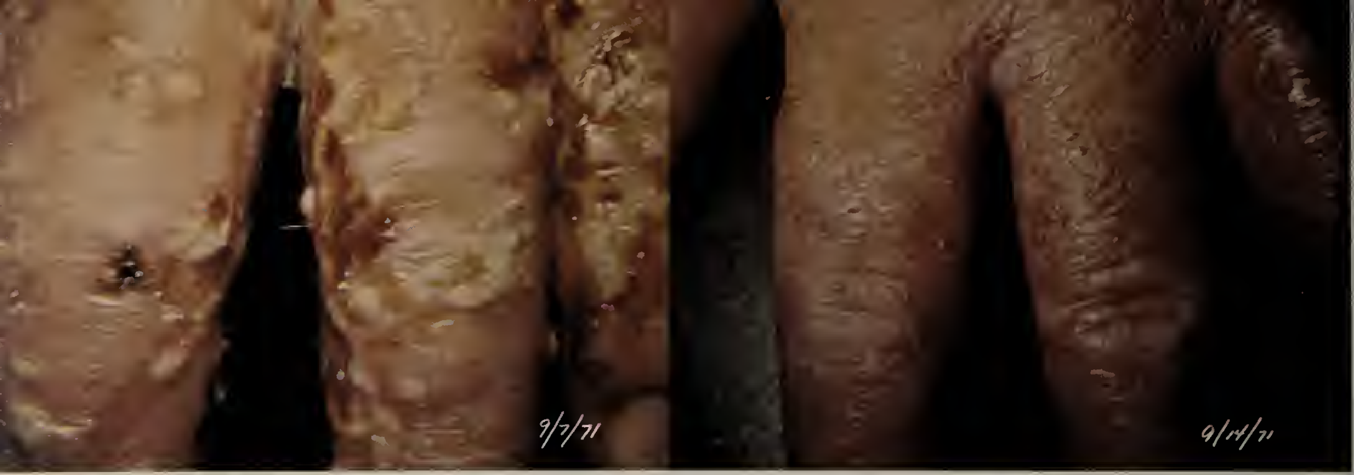

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Precautions: Use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, institute appropriate therapy. In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and blood serology repeated monthly for at least four months. Patients on anticoagulant therapy may require downward adjustment of such dosage. Test for organ system dysfunction (e.g., renal, hepatic and hemopoietic) in long-term use. Treat all Group A beta hemolytic streptococcal infections for at least 10 days. Avoid giving tetracycline in conjunction with penicillin.
Adverse Reactions: (Common to all tetracyclines, including MINOCIN) GI: (with both oral and parenteral use): anorexia, nausea, light-headedness, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in anogenital region. *Skin:* maculopapular and erythematous rashes. Exfoliative dermatitis (uncommon). Photosensitivity is discussed above ("Warnings"). *Renal toxicity:* rise in BUN, dose-related (see "Warnings"). *Hypersensitivity reactions:* urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus. When given in high doses, tetracyclines may produce brown-black microscopic discoloration of thyroid glands; no abnormalities of thyroid function studies are known to occur. In young infants, bulging fontanels have been reported following full therapeutic dosage, disappearing rapidly when drug was discontinued. *Blood:* hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia.
NOTE: *Concomitant therapy:* Antacids containing aluminum, calcium, or magnesium impair absorption; do not give to patients taking oral minocycline. Studies to date indicate that MINOCIN is not notably influenced by foods and dairy products.

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> *"The history of science, and in particular the history of medicine . . . is . . . the history of man's reactions to the truth, the history of the gradual revelation of truth, the history of the gradual liberation of our minds from darkness and prejudice."*
>
> *—George Sarton, from "The History of Medicine Versus the History of Art"*

Are combination drug products useful in treatment involving concomitant use of two or more drugs?

Opinion

Results of a questionnaire to 7,000 physicians:

62.9%
Believe combination drug products are useful.

13.8%
Do not believe combination drug products are useful.

Are combination drug products useful in treatment involving concomitant use of two or more drugs

Opinion & Dialogue

Doctor of Medicine

Louis Lasagna, M.D.
Professor and Chairman
Department of
Pharmacology & Toxicology
University of Rochester
School of Medicine
and Dentistry

Obviously, many drugs are given concomitantly. Whether it makes sense to combine medications in one preparation, be it capsule, tablet, or liquid, is a question that can be answered only by examining the advantages and disadvantages in the individual case.

Among the advantages is, first of all, convenience. The more medications that are taken concurrently and the more complicated the directions, the less likely the patient is to take medications accurately. From the standpoint of convenience and accuracy, and economy as well, you can make an important case for putting medications together in one preparation, as long as they are compatible.

By the same token, when you prescribe a properly tested and rational combination, you should have less worry about pharmaceutical or pharmacological compatibility – and about reasonable dosage ratios as well. Compatibility of the formulation should be demonstrated in the laboratory and clinic before the product is available for prescription—which is more than can usually be said for the physician's own spontaneous creations. And, the dosage ratios employed in rational precompounded combinations are designed to meet the needs of substantial numbers of "typical" patients.

There is no doubt that many "atypical" patients are to be found, and for them the prefabricated combination must be rejected. But that hardly argues for eliminating rational combinations from the market. Think, for example, of the problems that would arise if the components of widely accepted combinations, like the oral contraceptives and the diuretic-antihypertensives, always had to be prescribed, purchased and ingested separately.

One disadvantage that comes to mind is some doctors' unawareness of the ingredients a given combination contains. For example, a doctor might know that a patient is allergic to aspirin but forget that a certain analgesic mixture, which he knows only by its trade name, contains aspirin. His prescription, then, causes considerable discomfort, to say the least. This problem is a function of physician education, rather than of combination therapy as such. Improving doctors' knowledge about all medicaments they prescribe is a problem that deserves tackling on its own.

Another accusation leveled at combination drugs is that they encourage sloppiness of diagnosis and treatment. In many cases, however, a combination may prove to be the most effective choice. A good example of the usefulness of combinations appears in a recent article in the *Journal of Chronic Diseases* on the efficacy and side effects of an antihypertensive containing three ingredients, in which the track records of the combination drug and the individual ingredients were compared. Interestingly enough, whether the drugs were given individually or together, incidence and severity of side effects were the same. But blood pressure control was invariably better when the drugs were taken in one combination tablet than when they were taken separately (in "titratable" dosage) or in two or three different tablets.

Deciding which combinations constitute rational therapy obviously leads to a discussion of who is to determine which should be used and which should not. Realistically, I think combinations should be evaluated somewhat differently if they are old and established or new and untried.

In today's regulatory atmosphere, there is no possibility of a new combination being put on the market without a substantial amount of acceptable evidence in the form of controlled trials that show it to be safe and efficacious. On the other hand, I believe a different set of standards should apply to combination preparations that have been around for a long time. In other words, physician acceptance over a long period should be given some weight as evidence of the efficacy and safety of these drugs.

The FDA, however, does not seem to share this attitude. It often requires, for these older products, controlled trials that will monopolize the time of already overtired investigators and cost a great d
of money. I wish we cou
agree on a "grandfath
clause" approach to prep
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in making the ultimate d
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If two medications are ised effectively to treat a ertain condition, and it is nown that they are com- atible, it clearly is useful nd convenient to provide hem in one dosage form. t would make no sense, in act it would be pedantic, o insist they always be rescribed separately. To void the appearance of edantry, the "expert" de- ries the combination be- ause it is a fixed dosage rm. When the "expert" vokes the concept of fixed osage form he obscures e fact that single-ingre- ient pharmaceutical prep- rations are also fixed osage forms. By a singular emantic exercise he im- lies a pejorative meaning the term "fixed dose" nly when he uses it with espect to combinations. hat is ignored is the sim- le fact that only in the rest of circumstances oes any physician attempt titrate an exact thera- eutic response in his pa- ent. It is quite possible at some aches and pains ill respond to 500 mg. of spirin yet that fact does t militate against the *us- l* dose being 650 mg.

The other semantic ploy ten called into play is to escribe a combination roduct as rational or irra- onal.

Take antibiotic mixtures, e source of much of the iticism generated against combinations generally. Obviously, no one should be exposed willy-nilly to the potential side effects of two or three antibiotics when only one is needed. At the same time there are cases where it is prudent to prescribe more than one. The clinician is the judge in these circumstances, as he should be.

There is no clear definition of the word rational. Most persons, I suppose, would find it synonymous with reasonable, but in many circumstances it may best be defined as the opinion of those in power at the moment.

Other factors govern combination therapy, not the least of which has been its broad use by practicing physicians anxious to achieve convenience in prescribing, to reduce medication error, and to save money for their patients. Combinations clearly have met the test on all three counts.

I have been impressed by studies showing that the rate of error climbs markedly with the number of medications to be taken, even with sophisticated patients. When medically justified, therefore, this factor alone supports the logic of combination therapy.

The cost argument for combinations appears to be irrefutable. In 1971, R. A. Gosselin studied the 71 combination products (excluding oral contraceptives) among the 200 most prescribed drugs. The study found that if all 71 products were discontinued, and if each ingredient in these combinations were prescribed separately, the price of medicines to patients would jump by $443.2 million on a national basis! At a time when the cost of medical care is under so much fire, it would be nonsensical to boost costs without clearly irrefutable medical reasons.

The part played by government on this question, of course, is fundamental. The FDA should play a role in determining which combinations are reasonable. That role, as defined by law and regulation, is to ensure that any medication on the market is safe and effective in line with its label claims. Certainly combinations are entitled to as much consideration as single entities—neither more nor less. So long as the addition of one drug to another does not make either less safe, or less effective, so long as they are compatible in a formulation, we have a reasonable product. It makes no sense to recommend the use of two products for certain conditions and to deny their being combined in a single form. An unhappy side effect of the problem concerns the efficacy panel discussions of many products submitted for review. The term "effective, but" has been freely interpreted to mean "ineffective" in toto, regardless of the merit of the individual drugs. This interpretation has placed numerous useful combination products in needless jeopardy.

In reading the actual reports of the review panels, it seems clear that some of the ratings were based less on scientific research and clinical observation than on the "informed" opinions of the panelists. These "informed" opinions were accepted at face value, while the "informed" opinions of others who had used the products were rejected. All of this put combination products into a sort of scientific never-never land.

It should be kept in mind by all, government as well as others involved in our health care system, that advances in therapy are seldom made in leaps and bounds but rather by small painstaking steps—and that some of these steps have resulted from research in combination drugs as well as with single entities. Given the near-infinite biologic variation in patient response, this is hardly surprising to clinicians. It should not be to regulatory agencies either.

In the end, the practicing physician is in the best position to decide if a particular combination makes sense. Such a decision should not be made exclusively by those whose responsibility for continuing clinical care is limited. Clinicians are the best judges of efficacy because the ultimate proof of any product's effectiveness is acceptance by physicians who have observed its actions in patients over time. The corollary statement may be made about over-the-counter medicines, which would not long survive if they failed to afford the relief the user anticipates. That the antihistamine in a "cold" remedy may not *always* be necessary is no reason to proscribe the combination generally.

Opinion & Dialogue

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SCIENTIFIC ARTICLES

Tc-99m Labeled Red Blood Cells: A New Radiopharmaceutical for the Determination of Total Blood Volume and Blood Pool Scanning[*]

RICHARD C. REBA, M.D.[†], WILLIAM C. ECKELMAN, PH.D.[‡], AND SOLOMON N. ALBERT, M.D.[§]

The determination of red-cell volume is clinically useful to document the presence of polycythemia and in the pre- and postoperative management of the surgical patient. The red-cell volume determination rather than the plasma-volume determination is preferred for the estimation of the total blood volume because the total blood volume measurement may be less accurate when the plasma-volume determination is used.[1]

Technetium red-blood cells are less expensive to prepare than ^{51}Cr labeled cells because they can be prepared as needed in a clinical nuclear medicine department from an existing generator system. The radiation dose of the patient with ^{99m}Tc red cells is about one-tenth that with ^{51}Cr, an important consideration in children. Because of rapid physical decay, counting statistics and uniform dose are maintained when it is necessary to perform repeated studies.

An improved version of a previously published technique[2,3] has been developed so that rapid red-cell labeling can be accomplished with the patient's own blood. The advantages of the present method are decreased labeling time and increased reproducibility which are achieved by the elimination of the separation of plasma and red cells and by the use of larger volumes of pertechnetate and stannous chloride. In addition a citrate anticoagulant has been developed with strong buffering capacity which allows the stannous chloride to be stored in a strong acid solution. This allows the documentation of sterility and apyrogenicity before use which could not be done in the original procedure which required freshly prepared solutions.

Methods

The tin chloride is prepared in a nitrogen purged commercial glove box by adding 50 mg $SnCl_2 2H_2O$ to 0.43 ml of 11.4N HCl and diluting to 5 ml with sterile water. This stock solution is stable for two weeks. The aseptic addition of 0.1 ml of this solution to 5 ml of citrate (3% sodium citrate, 1% citric acid) results in a working solution containing 200 ug $SnCl_2 2H_2O$ per ml which is stable for eight hour.

The procedure is as follows: first, add $\leqslant 2$ ml TcO_4^- to 3 ml of citrate anticoagulant solution. Add the TcO_4^-/citrate solution to 5 ml of heparinized whole blood and gently mix for five minutes, then add 1 ml of tin citrate solution, and gently mix for one minute. Wash twice with 30 ml saline and re-suspend the labeled cells for injection. Two saline washes are usually sufficient to decrease the unbound technetium to less than 1%, and a third saline wash removes $<1\%$ of the activity. If 10% or more of the original activity is present in the second wash, the cells must be washed a third time before they can be used.

Red-blood-cell volume determinations were simultaneously compared with ^{51}Cr Rh_0Kell_0 and the subject's red cells labeled with ^{99m}Tc. Three ml whole blood samples and a 1:1000 dilution of the standard were counted in a 1.5 inch well crystal. The use of ^{99m}Tc permitted blood samples as small as 0.4 ml to be used with counting errors of less than 1% for a one minute count. Appropriate correction was made for ^{51}Cr Compton scattering detected in the ^{99m}Tc window.

Total blood volume was calculated by the indicator dilution formula

$$C_1 \times V_1 = C_2 \times V_2$$
$$V_1 = \frac{C_2 \times V_2}{C_1}$$

where $C_2 \times V_2$ is the total number of counts injected (C_2, concentration of the injected dose in counts per minute per ml and V_2, the volume injected), C_1 is the counts per minute per ml of the patient's blood at some time after the injection, and V_1 is the total volume into which the indicator (labeled red-blood cells) has been distributed.

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[*] This project was performed partly in the George Hyman Memorial Research Building at the Washington Hospital Center and supported by a research grant, The Development of Radiopharmaceuticals, from the Washington Hospital Center.

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The 15/30 minute ratio of radioactivity for ^{99m}Tc-RBC (1.03) was similar to that of ^{51}Cr-RBC (1.02) so for the purpose of this report the volume of distribution was compared at 15 minutes. Total blood volume rather than red-cell volume is presented.

Results

The results are presented in figure 2 and table 1. There is no significant difference between the volumes of distribution obtained by these methods. Likewise, the ^{99m}Tc total blood volume at 15 minutes and that calculated by extrapolation differ on the average by 3.3% or 151 ml., not a clinically significant difference. The average labeling yield was 41.7% but there was considerable variation, which was probably due to different protein affinities for reduced technetium. During labeling the red cells can be damaged by the addition of excess tin solution and effectively used for spleen scanning.[3] No free pertechnetate was found concentrated in the thyroid, salivary glands or stomach in those cases in which gamma camera images were taken.

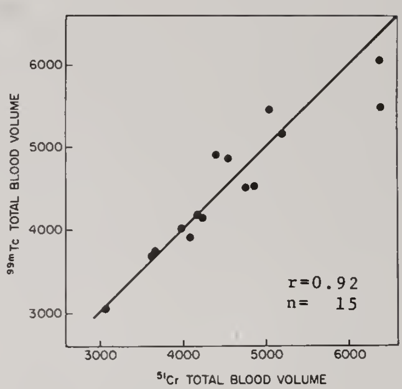

FIG. 2. Simultaneous total blood-volume determination comparing ^{99m}Tc labeled red-blood cells and ^{51}Cr labeled red-blood cells.

TABLE I: Comparison of Total Blood Volume (ml) Using ^{99m}Tc-RBC and ^{51}Cr-RBC

Patient	^{99m}Tc	^{51}Cr	Tc/Cr
GS	3898	4087	.95
EC	3054	3077	.99
MO	5468	5034	1.09
NC	4860	4546	1.07
MS	4017	3983	1.01
JB	4182	4175	1.00
CT	3688	3620	1.02
RS	4528	4848	.93
CG	6066	6373	.95
RJ	4930	4396	1.12
AM	3758	3670	1.02
JF	5154	5204	.99
FW	5476	6402	.86
AD	4504	4751	.96
VW	4145	4231	.98
		Average	1.00

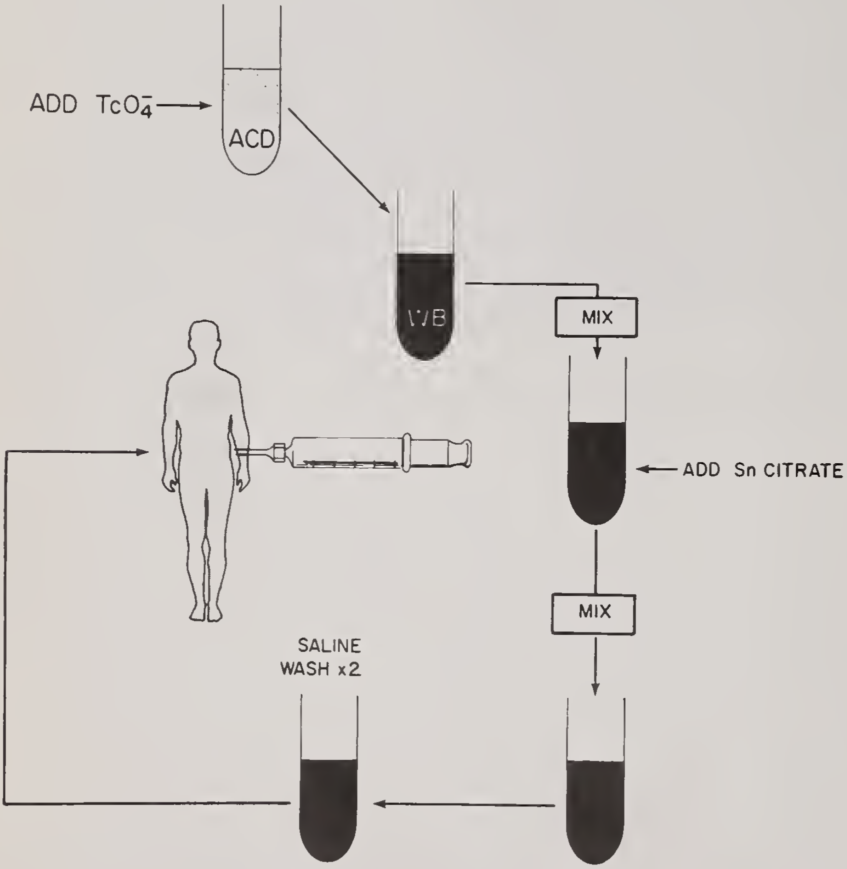

FIG. 1. Schematic representation of ^{99m}Tc red-cell labeling technique.

This preparation has also been used for blood-pool scanning, e.g., cardiac blood-pool for the determination of pericardial effusion (fig. 3), placental localization, and for vascular flow studies. It should be superior to ^{131}I-albumin for cardiac output determination, since the label remains completely confined to within the vascular compartment for at least two hours.

Discussion

A rapid, simple and efficient method for the preparation of ^{99m}Tc

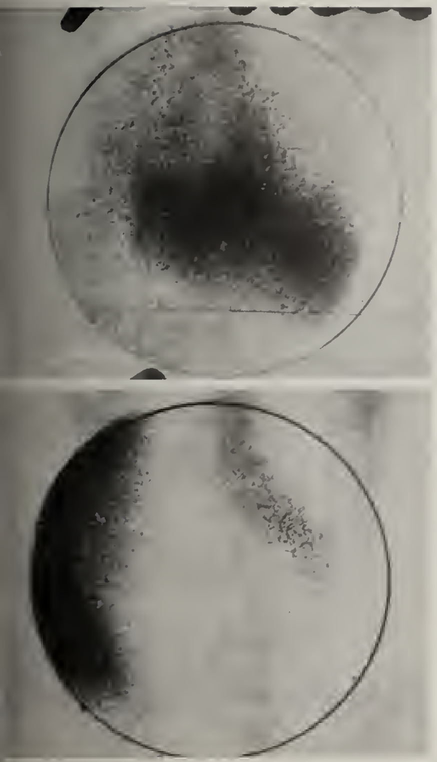

FIG. 3.(A) Intracardiac blood-pool scan performed with ^{99m}Tc labeled red-blood cells. When this image is directly compared to a transmission scan of the chest, (B) the final interpretation was that the enlarged cardiac silhouette was due to ventricular hypertrophy and/or dilatation without evidence of pericardial effusion.

red-blood-cells for the determination of red-cell volume has been clinically tested and found to be equivalent to the presently used ^{51}Cr red-blood-cells. In this study each patient's red-blood-cells were obtained and individually labeled with technetium 99m. However, we have also labeled Rh$_0$Kell$_0$ cells with ^{99m}Tc and compared this single preparation with ^{51}Cr Rh$_0$Kell$_0$ cells in a series of patients.[4] An excellent correlation was found.

The reported method of preparation offers distinct advantages because the tin-reducing solution can be prepared as a stock solution and the labeling procedure can be completed in 30 minutes. This procedure is preferred for pediatric patients because of the low radiation dose of ^{99m}Tc. The technique is also useful for blood-volume determinations in small animals because of good counting statistics and rapid physical decay of the ^{99m}Tc isotope which allows for small blood samples and repeated studies.

Summary

An improved method of labeling red-blood-cells with ^{99m}Tc has been developed. This method uses a citrate anticoagulant with strong buffering capacity and requires 20 to 30 minutes to complete. Only two centrifugation steps are required, and approximately 40% yield is obtained.

Red-cell and total blood volumes were determined in 15 patients with ^{99m}Tc and ^{51}Cr. The difference between individual measurements was not clinically significant. The labeled red-blood-cell technique can also be used for blood-pool scanning or flow studies. This radiopharmaceutical is the best available for studies in pediatric patients because of the low radiation dose of ^{99m}Tc. It is also advantageous because of the good counting statistics and rapid physical decay of the ^{99m}Tc isotope which allows for small blood samples and repeated studies.

Acknowledgment

The authors wish to express their appreciation to Mr. Ralph Will for his technical assistance.

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Quantitative Excretion of Senokot in Human Breast Milk*

MILTON W. WERTHMANN, JR., M.D. AND STEPHEN V. KREES, M.S.

Abstract: Nursing mothers are frequently given Senokot as a laxative in the post-partum period. To evaluate the potential absorption and excretion of Senokot in human milk, 25 mothers collected serial samples of breast milk after a standard oral dose of Senokot. Fifteen of the mothers had effective catharsis. No sample of breast milk had detectable levels of Senokot. Two infants of the 15 symptomatic mothers and one infant of the 10 asymptomatic mothers experienced a definite change to loose stools. Repeat study with the three mothers of symptomatic nursed infants using double dose Senokot resulted in no laxative effect on the infants and no detectable Senokot in the breast milk. Senokot appears to be a safe laxative for use by nursing mothers.

Most mothers in the post-partum period are given some form of laxative. Senokot, a complex diglycone composed of Sennoside A and B, is a frequent choice of obstetricians. After several inquiries by anxious mothers on the post-partum floors reporting brownish discoloration of breast milk after ingestion of Senokot and pronounced catharsis of the nursed infants, a search of the literature was undertaken to determine the potential for transport of Senokot into breast milk. The only study in humans was reported in 1963 by Baldwin.[1] This study included 50 nursing mothers who ingested Senokot. The nursed infants had no noticeable catharsis. The study was not designed to measure the excretion of Senokot in breast milk. Therefore, it was determined to attempt to assess the quantitative excretion of Senokot in human breast milk in our research laboratory.

Method

Twenty-five volunteer mothers ranging in age from 23 to 36 years comprised the test group. At the time of the study these mothers had been nursing an average of 4.7 months (2½ to 15 months). Thirteen were nursing their first child and 12 were nursing the second, third or fourth child. All mothers were in good health. During the test no alcoholic beverages or drugs were ingested. During the study all the mothers eliminated from their dietary intake any foods known to cause loose stools. Mothers were given the option to continue to nurse or to substitute formula during the test period. Twenty-three of the five mothers elected to continue to nurse their infants. None of the nursed infants received anything other than breast milk during the test period.

A standard dose of Senokot (100 mg tablet containing 8.602 mg of Sennosides A and B)[2] was ingested by each mother and the time of ingestion noted. Breast milk was expressed from one breast and collected over the next six hours at half-hour intervals and kept refrigerated. Infants were nursed exclusively from the other breast. Number and type of stools for the mother and the infant for the subsequent 24 hours were recorded.

Method of Analysis

The analytical method employed is based on that of J. Lemli[3] for the colorimetric estimation of anthraquinones formed by the oxidation of sennosides A and B to rhein. To 25 ml of milk was added 25 ml of 16.6% (w/v) ferric chloride solution. The solution was refluxed for 30 minutes and cooled. Five ml of concentrated hydrochloric acid was added, and the reaction mixture was refluxed for an additional 30 minutes.

The reaction solution was cooled, transferred to a separatory funnel, and extracted with three 50-ml portions of ether. Centrifugation was necessary to separate the layers. The ether was then back-washed with distilled water.

One hundred ml of the ether layer was removed and mixed thoroughly for three minutes with 5 ml of 1N KOH. The rhein potassium salt thus produced in the aqueous layer was measured within a period of five minutes at 510 nm with a suitable spectrophotometer with 1N KOH as a blank.

Since some samples of milk showed variable blank values when measured at 510 nm, internal standard samples

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were used. These were prepared by adding 0.1 ml of an 8.6 mg% aqueous solution of sennosides A and B to 25 ml of milk obtained from each subject prior to ingestion of the Senokot tablet. This sample was treated in the same manner as described above.

A direct comparison was then made between the unknown sample and the sample with the internal standard (0.34 mcg. Sennoside A and B/ml). None of the 25 samples of breast milk had detectable amounts of Sennoside A or B. During the study period 10 mothers had a definite change to loose stools and five had "gas" cramps. Ten mothers reported normal stools. Of the 15 mothers reporting loose stools, two nursed infants had loose stools while 13 had normal stools. Of the 10 mothers with normal stools, one infant developed loose stools. Repeat double-dose Senokot ingestion by the mothers whose nursed infants had loose stools resulted in still no detectable Sennoside in their breast milk nor did loose stools occur in these nursed infants on the second test.

On occasion the occurrence of loose stools in breast-fed infants related to the maternal ingestion of certain foods is well known. The ingestion of a known cathartic could well be blamed for loose stools in nursed infants. However, in this supervised clinical study involving healthy mothers with carefully restricted diets, although a clinical change in maternal catharsis occurred in 60% of the volunteer mothers, in no case was Senokot detected in amounts equal to or greater than 0.34 mcg Sennoside A and B ml in their breast milk. This study then confirms quantitatively the previous clinical study of Baldwin.[1] The probability of an infant ingesting even 1 mg of Senokot via breast milk in a 24-hour period is extremely unlikely. We are unable to causally implicate Senokot ingested by a nursing mother with catharsis in the breast-fed infant.

Acknowledgments

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Spectrum of Bowel Disease Associated with Use of Oral Contraceptives*

DAVID A. MOROWITZ, M.D. AND BARRY H. EPSTEIN, M.D.

The widespread use of oral contraceptives has been followed by increasing reports of significant unfavorable side-effects. Included among these are intravascular thromboses and emboli, often resulting in pulmonary or cerebral infarction. Disease of the gastrointestinal tract or its vasculature has not been fully appreciated as a complication. During the last two years we have encountered two cases of bowel infarction and three of inflammatory bowel disease in previously healthy young women that may have originated from the use of these drugs. Recent reports of similar cases and the potential significance of these observations prompts their detailed description.

Report of Cases

Case 1. A 28-year-old white woman had been in good health for her entire adult life. After the birth of her fourth child she began to take oral contraceptives (norethindrone-mestranol, Ortho-Novum-1®) and was well for the next 17 months. Then she suddenly developed increasingly severe mid-abdominal pain associated with frequent, blood-tinged, watery stools. This continued for six days, and on arrival at the hospital she appeared acutely ill with hyperactive bowel sounds and diffuse abdominal tenderness. Proctoscopic examination disclosed a normal rectal and sigmoid colon mucosa, but bloody material was seen coming from above the tip of the instrument. Gastric aspirate contained small amounts of digested blood. The patient's abdominal pain and bloody stools continued, but despite signs of worsening hypovolemia the hematocrit rose from 40 to 56 vol.% over the next 24 hours. The possibility of intestinal infarction was considered, and at operation several loops of gangrenous, distended, fluid-filled jejunum and ileum were found. There was no evidence of volvulus or malrotation of the gut. Several major branches of the superior mesenteric vein were totally thrombosed (fig. 1); the mesenteric arteries were normal. The diseased bowel was resected and a primary jejuno-ileal anastomosis performed. The patient's postoperative course was complicated by recurrent intestinal bleeding, and she was re-explored eight days after the initial operation. An additional segment of gangrenous ileum was found at the anastomotic site and was resected. The entire remaining small bowel distal to the ligament of Treitz measured 19 inches. Despite a pulmonary embolism after her second operation she recovered completely with mild diarrhea and malabsorption of Vitamin B_{12} as her only residual problems. During and after hospitalization no other clinical or laboratory evidence of hypercoagulability, collagen-vascular, or primary cardiovascular disease was found. There had been no history of trauma to the abdomen.

Case 2. A 20-year-old unmarried white woman was in excellent health until October 1966 when she began to use oral contraceptives (ethynodiol diacetate-mestranol, Ovulen-21®). There had been no previous history of bowel disease of any kind. On the sixth day of her first anovulatory cycle, she developed severe lower abdominal cramps, fever and diarrhea but continued to take medication for two weeks. Continued illness prompted hospitalization, and proctoscopic examination and rectal biopsy revealed changes consistent with acute ulcerative colitis. Barium studies disclosed deep ulceration and thickening of the terminal ileum and ascending colon consistent with granulomatous ileocolitis. Discontinuation of the contraceptives was followed promptly by a decrease in the frequency and severity of the symptoms, but continued low-grade abdominal pain and fever over the subsequent eight months prompted the use of nonabsorbable sulfonamides and intermittent courses of systemic corticosteroids. Except for a normal platelet count and prothrombin time, coagulation studies were not performed. X-ray films one year after the initial episode showed no significant change, and the patient continued to be in good health for another year, but with flareups of symptoms requiring two additional hospitalizations. Evaluation in 1970 showed completely normal GI X-ray examinations with patient taking no medications, including oral contraceptives.

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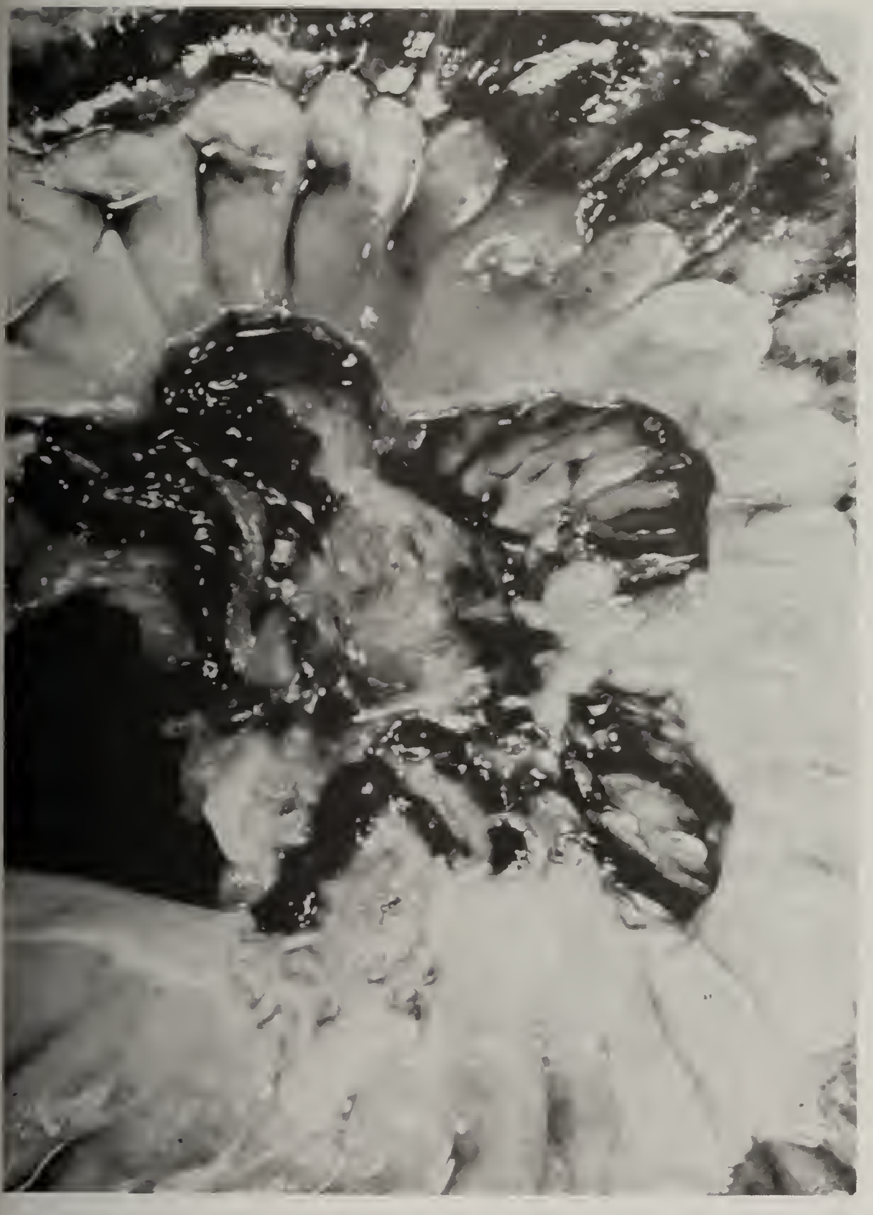

Fig. 1. Resected specimen of jejunum and ileum in patient 1 showing ischemic necrosis of bowel wall and well-organized adherent thrombi totally occluding adjacent mesenteric veins.

Case 3. Twelve hours prior to her hospitalization a 38-year-old white woman was awakened by a severe, cramping, mid-abdominal pain, followed by passage of a voluminous, bloody stool. The pain improved but was replaced by a persistent left lower-quadrant aching. For six years she had been taking a variety of oral contraceptives, including Ovulen® most recently. Examination disclosed only left lower-quadrant adbominal tenderness. Blood was seen in the rectum and sigmoid colon at proctoscopy but the mucosa was normal. Barium enema (figs. 2a and b) disclosed an irregularly narrowed area six inches in length in the mid-descending colon. The mucosa there appeared edematous with "thumbprinting" changes and loss of haustrations. No ulcerations were seen. Examination of the stomach and small intestine was negative. Pathogenic bacteria and parasites were not found in the stools. Bleeding and clotting times, platelet counts, prothrombin and partial thromboplastin times were normal. A transfermoral inferior mesenteric arteriogram performed on the day following the barium enema revealed hypervascularity and thickening throughout the involved segment of colon (figs. 3a and b). Though no major arterial or venous occlusions were seen, the marked tortuosity of vessels suggested collateral re-vascularization at the terminal arcade level, consistent with a local thrombosis.

The bleeding and pain stopped over the 72 hours following admission, and the patient was discharged after 10 days. The birth control pills were stopped. Four weeks later the barium enema was completely normal. She has remained well since.

Case 4. A 22-year-old white married woman was in excellent health six weeks after delivery of her child. Oral contraceptives (Ovulen®) were given, and she felt well until soon after her second anovulatory menstrual cycle, when she developed fever, cramping abdominal pains, and diarrhea. Proctoscopy disclosed moderate granularity and edema of the rectal mucosa; barium enema and small bowel x-ray examination were normal. Rectal biopsy revealed a dense mucosal inflammatory infiltrate with focal hemorrhage and crypt abscesses. Except for a persistent leukocytosis the remainder of the laboratory evaluation including coagulation studies was normal. The patient discontinued oral contraceptives and was begun on sali-

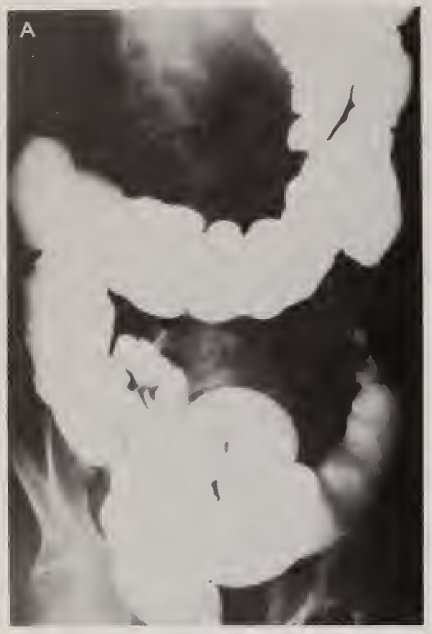

Fig. 2a. Barium enema showing well-demarcated narrowing in the mid-descending colon. Remainder of large intestine appears normal.

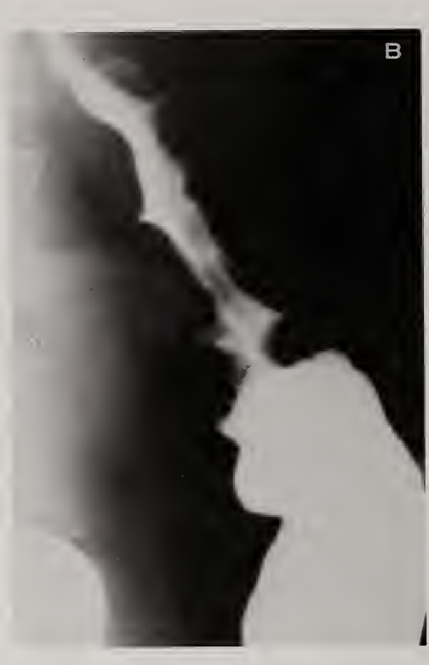

Fig. 2b. Spot films of abnormal area in figure 2a shows long, stenotic segment with irregularly rounded edema of the mucosa, so-called "thumbprinting".

cylazosulfapyridine, 4 gm/day and 100 mg hydrocortisone enema with initially favorable results, but she was lost to follow-up over the ensuing 11 months. She returned in April, 1969, complaining of recurrent diarrhea, abdominal pain, and weight loss, following resumption of birth control pills. At the time she appeared chronically ill and wasted. Proctoscopic examination disclosed active mucosal bleeding and friability. Barium enema (Fig. 4) revealed deep ulcerations and loss of haustral markings over the entire colon. Discontinuance of oral contraceptives was followed by partial improvement. Later prednisone, 40 mg/day, was begun with a dramatic disappearance of her symptoms, return of sense of well-being, and rapid weight gain. The proctoscopic appearance of the rectum returned to normal over the next two months. The patient has remained well on slowly declining steroid doses without resuming oral contraceptives.

Case 5. Except for a history of asymptomatic rheumatic heart disease this 33-year-old white woman was well until 1965, when she developed diarrhea and was found to have iron-deficiency anemia. Complete gastrointestinal X-ray examinations and sigmoidoscopy revealed only hemorrhoids, and the anemia was attributed to the latter and known menorrhagia. The patient was taking Ortho-Novum® at that time. One year later, having discontinued all drugs, she underwent an elective hemorrhoidectomy, at which time barium and endoscopic examination of the colon were negative. She remained well until April, 1967, when, three months after having begun mestranol-cholormadinone (C-Quens®), she developed abdominal cramping, tenesmus, and blood mucoid diarrhea. At that time physical examination revealed pallor, left-sided abdominal tenderness, and apical systolic and diastolic heart murmurs. Electrocardiogram and chest X-ray films were normal. Proctoscopic examination disclosed an acutely edematous and friable rectal mucosa with active bleeding. Colon X-ray examinations demonstrated fine mucosal ulcerations of the descending colon. The patient was begun on salicylazosulfapyridine, and her oral contraceptives were discontinued. Thirteen days later the rectal mucosa showed only minimal edema, and 21 days after that it appeared completely normal. Following discharge from the hospital she was maintained on sulfonamides but against medical advice resumed use of C-Quens®. Nineteen days after doing so, abdominal pain and bloody diarrhea recurred, and barium enema and proctoscopy again indicated acute ul-

Fig. 3a. Inferior mesenteric arteriogram in patient 3 reveal increase in number and tortuosity of small arterioles over areas between corresponding with the stenosis seen in figure 2. An increased capillary stain indicates thickening of the wall.

cerative colitis. After re-hospitalization, both sulfa drugs and oral contraceptives were discontinued, and she was treated only with diphenoxylate and atropine (Lomotil®) for control of diarrhea. She became asymptomatic in 10 days with complete return to a normal appearing rectosigmoid mucosa. She was last seen in July, 1969, and was well, taking no medications.

Comment

Until recently, development of abnormal liver function tests was felt to be the major gastroenterologic side-effect of oral contraceptives. Now, thrombosis of abdominal vessels in previously healthy persons has been described in several recent reports. Kilpatrick et al[1] noted two women, aged 29 and 32, who developed abdominal pain and bloody diarrhea while taking oral contraceptives. Their symptoms began in 47th and 2nd month of therapy, respectively and were associated with barium X-ray evidence of bowel infarction, including narrowing of the lumen, spasm, and "thumbprinting." In both patients discontinuing the anovulatory agent was followed by disappearance of symptoms and a return of the X-ray examinations to normal. Ward and Stevenson[2] recorded a case similar to those of Kilpatrick and likewise concluded that the intestinal abnormalities and the use of oral contraceptives were related. Brennan, Clarke, and Macbeth[3] subsequently recorded the cases of two women, aged 38 and 45, who developed thrombotic occlusion of the superior mesenteric artery while on birth control pills for 48 and 11 months respectively. Both patients required surgery, but gangrene of the entire small intestine in their first patient precluded resection, and she ultimately died. Their second patient

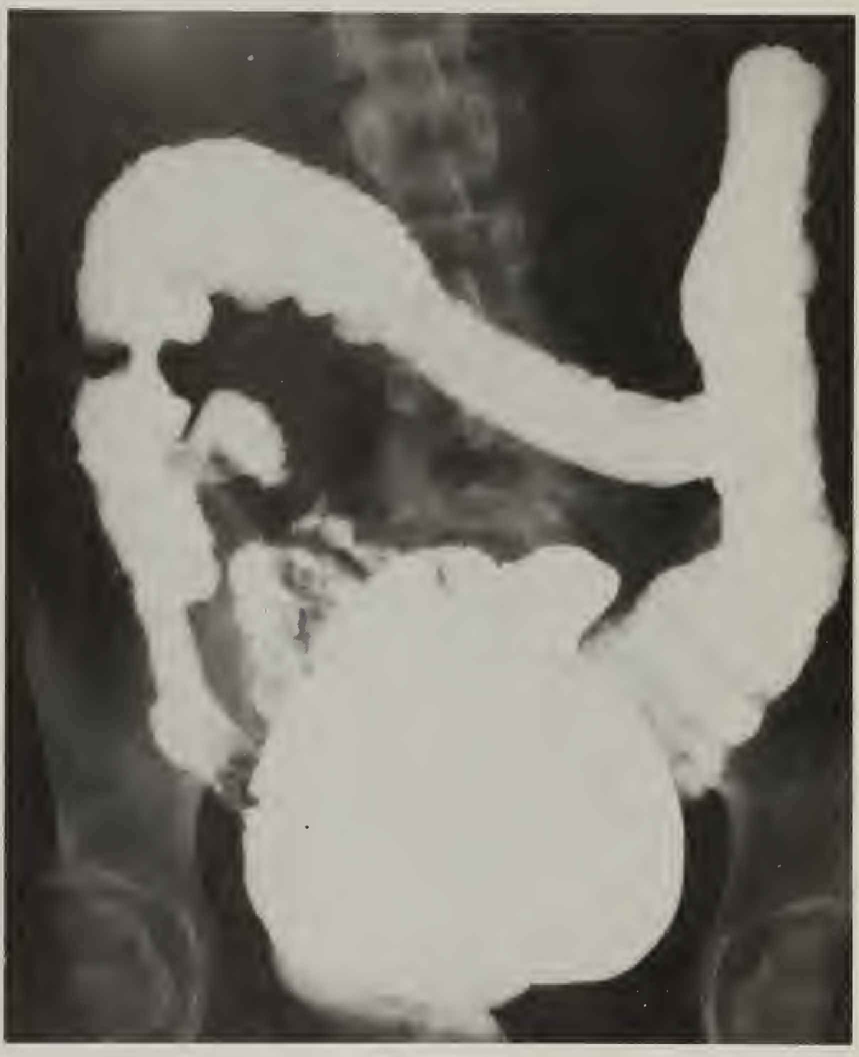

Fig. 4. Barium enema of patient 4 reveals numerous, irregular deep ulcerations over the entire length of the colon, with marked loss of haustrations.

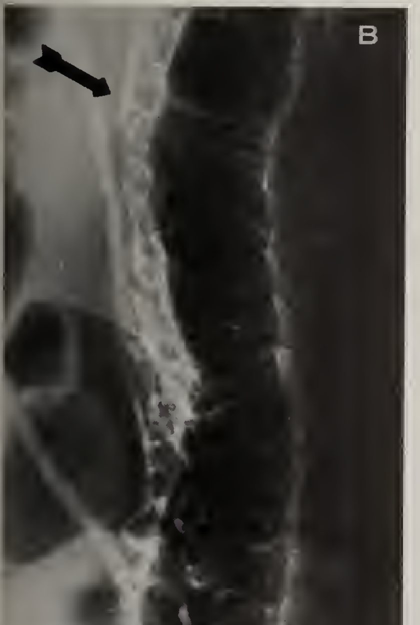

Fig. 3b. In venous phase proliferation and tortuosity of small vessels seen again suggesting infarction of the microvasculature or hemorrhage into bowel wall.

required removal of the distal jejunum, ileum and ascending colon. There was no evidence of underlying hematologic or cardiovascular disease in either patient.

Additional reports have described thromboses of superior and inferior mesenteric arteries,[4-6] celiac arteries,[7] and inferior mesenteric[8,9] and hepatic veins,[10-13] all occurring in previously healthy persons taking oral contraceptives. The relationship of the drug to the illness in these cases appears established.

The role of oral contraceptives is more speculative in the patients whose illness suggested acute ulcerative or granulomatous colitis. The large numbers of patients taking these drugs and the relative frequency of inflammatory bowel disease in women of child-bearing age suggest a fortuitous relationship. However, in cases 2, 4 and 5 the onset of colitis closely followed the initial use of these drugs, and in case 5 their sporadic use was followed by exacerbations of illness. Likewise, each patient improved when these drugs were withheld. Since the major pathogenicity of anovulatory agents derives from their effect on thrombogenesis, we question whether the chronic type of bowel disease seen here might not have begun as a bowel infarction secondary to a hypercoagulable state and continued through an unknown, perhaps immunologic mechanism as colitis. The evidence for this is highly speculative. Though we could not find any evidence of hematologic disease in our cases, persons with inflammatory bowel disease often have clinically significant hypercoagulability with venous and arterial thromboses and emboli.[14] Elevations of circulating clotting factors, notably AHF and platelets,[15,16] have also been described. A role of vascular factors in enterocolitis is also suggested by the frequent histologic finding of submucosal edema, bowel-wall thickening, hemorrhage, and venous and lymphatic dilatation. Last, the clinical pictures of ischemic and inflammatory bowel disease are frequently similar, though the former is typically an acute, usually reversible phenomenon. In the second case of mesenteric arterial occlusion reported by Kilpatrick, et al,[1] sigmoidoscopic evidence of ulcerative colitis was present, and the physicians caring for her were sufficiently convinced of that diagnosis to initiate ACTH and corticosteroid therapy. Likewise, in the patients with bowel infarction reported by Barjian[8] and Lowry et al[4] a diagnosis of regional enteritis was made before the discovery of the vascular problem. Silberstein[17] reported a case of severe diarrhea that was remitted only when oral contraceptives were discontinued.

Since the cause or causes of inflammatory bowel disease are unknown, the final decision as to the role of oral contraceptives in both types of colitis described above awaits future reports and further study. Until then, we would urge obtaining a history of the use of anovulatory agents in woman with symptoms of intestinal disease, and suggest a potential beneficial effect by their discontinuance.

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Total Body Asanguineous Hypothermic Perfusion and Blood Volume Exchange in Dogs*

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KAREL B. ABSOLON, M.D., PH.D.

Removal of the total circulating blood volume and temporary replacement with an asanguineous perfusate under hypothermic conditions has been suggested as a method of treatment for acute hepatic insufficiency.[1] During the asanguineous stage neglible amounts of hemoglobin circulate with a consequent tissue hypoxia. The combination of dissolved oxygen in the perfusate and a decreased metabolic demand under hypothermia allows the organisms to survive. The final step is the replacement of the asanguineous perfusate with whole blood.

This experimental technique may provide a practical method of removing from the circulatory system various nondialyzable toxic substances accumulated through oral or intravenous administration or as a result of abnormal metabolic functions.

The present study concerns the hemodynamic and biochemical parameters in normal dogs prior to, during, and after asanguineous perfusion.

Materials and Methods

Six adult mongrel dogs were anesthetized with intravenous sodium nembutal (30 mg/kg), intubated and kept on positive pressure ventilation with 98% oxygen and 2% carbon dioxide. Catheters were inserted in the aorta and vena cava through neck vessels for direct monitoring of arterial blood pressure and central venous pressure. A prove† for continuous pO2 monitoring was placed in the carotid artery. ECG needle electrodes were attached to the extremities. A rectal probe connected to a tele-thermometer monitored the core temperature constantly.

Dissection and cannulation of the femoral vessels was performed utilizing an 18 fr. venous cannula 30 cm. in length for drainage of blood and a 12 fr. cannula was inserted in the femoral artery for infusion.

Base-line blood samples were taken for CBC and blood gases. Cardiac output measurements were performed pre-operatively and postoperatively, utilizing the dye dilution technique.‡ Blood volumes and extracellular compartment studies were obtained preoperatively and postoperatively by means of Cr^{51} tagged red cells, I^{131} human serum albumin, and S^{35}.[2] Total asanguineous perfusion and replacement with donor blood was accomplished with a heart-lung pump consisting of two modular pumping heads, two adult, and one pediatric oxygenator.§ A circuitry was designed to integrate the three oxygenators.

Blood exchange was begun by removing occluding clamps on the venous and arterial lines. The animals were exanguinated into one reservoir while simultaneous infusion of perfusate from the second reservoir was started. The perfusate was composed of a 1:1 dilution of Ringers' Lactate and Dextran 70¶ solutions cooled to 27°C. The rate of exanguination and infusion was controlled so as to maintain venous pressures close to normal limits. Blood samples for hematocrit and hemoglobin were drawn periodically until exanguination was completed. Whole fresh, warm donor blood (ACD) was infused at this stage through the arterial line, replacing the perfusate. Five hundred mg of Methylprednisolone was administered to obviate an allergic reaction.

The animals were kept on partial bypass until the core temperature reached normal values. After cannulas and catheters were removed and the wounds closed the animals were returned to their cages.

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† IBC In Vivo Oxygen Catheter; International Biophysics Corp., Irvine, California.

‡ Model 103-IR Cuvette Densitometer; Model 104-A Dye Curve Computer; Gilford Instrument Laboratories, Oberlin College, Ohio.

§ Bently Laboratories, Santa Ana, California.

¶ Cutter Laboratories, Berkeley, California.

Results

Five out of six dogs subjected to total body asanguineous perfusion were longterm survivors. Gross and microscopic tissue examination showed no pathology. One death was the result of anaphylactic shock due to a transfusion reaction.

Blood pressures ranged from 130/80 mm/Hg to 80/60 mm/Hg (av 110/80 mm/Hg) pre-operatively and showed a drop at the beginning of the procedure, ranging between 100/45 mm/Hg to 40/20 mm/Hg (av 65/30 mm/Hg) at the end-point of the asanguineous hypothermic stage. Immediately after replacement with whole blood, systolic and diastolic pressures returned toward normal, but remained lower than pre-operatively, ranging from 120/80 mm/Hg to 50/30 mm/Hg (av 90/40 mm/Hg).

Central venous pressure was the most practical index of fluid-volume balance. The drop in the blood pressure correlated with a rise in CVP and a decrease in cardiac output. Operative blood chemistries were related to the hemodilution. The hematocrit values decreased to an average low of 3.3% (1.0% to 7.1%), returning to an average of 15.5% (9.8% to 21.9%) after exchange.

Cardiac outputs, measured preoperatively and within one hour of the completion of the exchange, showed a drop from an average 2. 35 L/min. (1.8 L/min to 2.5 L L/min) to an average of 2.00 L/min. (1.2 L/min to 2.1 L/min) postoperatively.

The positive gain of an average of 228 ml (13%) of the exchanged volumes was measured. The blood volumes showed a decrease of the red-cell mass after perfusion. The red-cell mass after perfusion. The red-cell volume deficit was calculated to be on the average 268 ml, 48% of preoperative. Conversely, the total plasma volume was expanded to an average of 496 ml, 41% above pre-operative.

S-T segment depression and T-wave inversion were seen in the electrocardiogram of three experimental animals throughout the duration of the asanguineous perfusion. These ECG findings were observed for several hours postoperatively but invariably returned to normal. An increase of myocardial irritability and dysfunction was suggested by the various types of arrhythmia, which included bradycardia, to rates of 30 to 40 beats a minute, and ventricular extrasystoles. In one dog this led to ventricular tachycardia and fibrillation, which was readily converted to normal sinus rhythm with D.C. shock. A decreased cardiac output, an expression of myocardial failure observed at the end of the perfusion, responded to the intravenous administration of Isoproterenol, 0.2 mg. to 0.3 mg. Calcium gluconate was added at the end of the procedure to improve myocardial contractility and neutralize the citrate of the replaced blood.

Discussion

Previous studies have proved that under hypothermia the oxygen demands of tissues are reduced and the oxygen dissociation curve of the hemoglobin is shifted to the left, resulting in favorable conditions for supporting life in an anoxic environment.[3] Neely et al[4] were able to maintain dogs perfused with an anoxic bloodless solution up to 20 minutes with a considerable survival rate. Similarly, Klebanoff et al[1] reported the clinical application of the total body asanguineous perfusion for the treatment of stage four hepatic coma.

The average duration of the a-sanguineous exchange in the present experiment was 16 minutes, ranging from 10 to 30 minutes. The utilization

TABLE I: Average Values of Hemodynamic and Biochemical Indices

	Prior to Perfusion	During early Perfusion	End of Perfusion	After Perfusion
B/P	110/80 mm/Hg	97/53 mm/Hg	65/30 mm/Hg	90/40 mm/Hg
TEMP	37°C	35°C	28°C	33°C
CVP	7 mm/H_2O	12 mm/H_2O	24 mm/H_2O	13 mm/H_2O
pO2	269 mm/Hg	525 mm/Hg	460 mm/Hg	322 mm/Hg
pCO2	21.5 mm/Hg	22.1 mm/Hg	7.3 mm/Hg	17.2 mm/Hg
pH	7.37	7.32	7.27	7.48
Hct	35%	17.5%	3.3%	15.5%
Hgb	12Gm%	4.6 Gm%	1.0 Gm%	5.2 Gm%
RCV	551 ml	–	–	283 ml
PV	1203 ml	–	–	1699 ml
TBV	1754 ml	–	–	1982 ml
C.O (See text)	2.5 L/min	–	–	2.1 L/min

of a long venous cannula reaching to the right atrium provided satisfactory venous return in every experiment; it is useful to reduce the asanguineous period and with it the associated hypoxia to tolerable limits. The observed decrease of the red-cell mass after perfusion did not affect the recovery of the animals and was spontaneously corrected in a 24-hour period, suggesting hemodilution and splanchnic pooling.

Extracellular fluid shift during the total exanguineous state suggests both expansion and contraction and is presently under study. The necessity to include Dextran 70 in the perfusate was exemplified in one experiment. Massive outpouring of fluids in this animal, in whom the blood volume was replaced with only Ringers' Lactate, resulted in shock associated with acute ascites, muscular rigor, hypotension, and rapid death.

A tendency to awake from the anesthesia was invariably observed, suggesting the removal of the circulating barbiturate. A temporary increased muscle tone was another constant finding, and together with fasciculation of the muscles was another indication of the decreasing depth of anesthesia that required additional administration of the anesthetic agent. The re-appearance of reflexes previously depressed, such as corneal and pupilary, was a constant finding.

This study deliniates the biochemical and hemodynamic changes observed during asanguineous perfusion and demonstrates the safety of the technique of asanguineous exchange as developed in this laboratory. It is hoped that total asanguineous blood exchange may be developed so as to be utilized for maintainance of patients in chronic and acute liver failure and after liver transplantation.[5]

Asanguineous perfusion as documented in this study indicates that the method may prove valuable as a supportive measure in certain clinical entities, such as acute fulminating hepatic failure, endotoxic shock, and in those toxic conditions in which the toxic agents cannot be dialyzed by the current methods.

Acknowledgment

The authors wish to acknowledge the technical assistance of Mr. Norman R. Baker and Mrs. T. Fay Totero.

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Intra-Gastric Rupture of a Splenic Artery Aneurysm.*

JERRY B. ROGERS, M.D. AND JEROME W. CANTER, M.D.

The diagnosis of massive upper gastrointestinal bleeding from an obscure source continues to plague clinicians.

Extra-alimentary tract sources of massive upper gastrointestinal bleeding are often overlooked and deserve repeated emphasis. One such source is a spontaneous arterio-enteric fistula. The high mortality associated with this entity makes early diagnosis imperative. The present report illustrates the course of such a fistula and emphasizes the difficulties encountered in the absence of an accurate diagnosis.

Report of Case

C. M., a 54-year-old man, was admitted to the Washington Hospital Center on December 13, 1970. He was previously admitted in July, 1967 for acute pancreatitis and a possible pancreatic pseudocyst. He remained well until several hours prior to his present admission when he experienced the sudden onset of mild epigastric discomfort, vomited about a quart of bright red blood and fainted. On admission his blood pressure was 120/70 mm Hg with a pulse of 86 per minute. The hematocrit was 22% and hemoglobin 6.8 gm. Liver function tests and coagulation studies were within normal limits. Serum amylase and lipase were normal. A nasogastric tube was inserted into the stomach, but no blood was obtained on irrigation. Esophagoscopy and gastroscopy revealed no abnormalities. Emergency upper gastrointestinal series demonstrated an extrinsic pressure defect upon the fundus of the stomach unchanged since 1967 (figs. 1 and 2). There were no intrinsic abnormalities in the stomach or duodenum. He received 2,000 ml. of whole blood over a 48-hour period. Another upper gastrointestinal series again failed to demonstrate the source of bleeding. A second gastroscopy failed to reveal any significant mucosal abnormalities in the esophagus or the stomach. Operation was advised, but the patient refused and was discharged on the sixth hospital day.

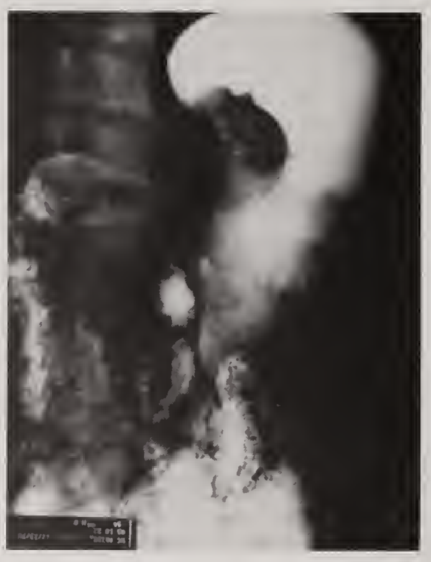

FIG. 1. Antero-posterior view of the stomach demonstrating compression of fundus.

Six days after discharge the patient again experienced epigastric discomfort followed by hematemesis and syncope. In the Emergency Department the blood pressure was 120/80 mm Hg with a pulse of 92. The initial hematocrit was 36% and hemoglobin 11.3 gm. but two hours later the hematocrit was 31% and hemoglobin 9.9 gm. During the subsequent 48 hours he was transfused with one unit of whole blood and four units of packed cells, which increased the hematocrit to 38%. A nasogastric tube inserted while the patient was in the

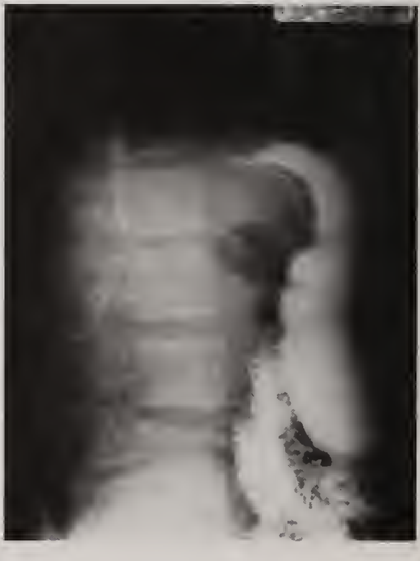

FIG. 2. Lateral view of stomach demonstrating gastric compression.

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Emergency Department initially returned coffee-ground material which was hematest positive, but within one hour the gastric return was clear. An attempt to locate the site of bleeding by arteriography was considered on the day following admission but was deferred because the patient had stopped bleeding. Operation was again proposed to the patient but he remained resistant. On the sixth hospital day he experienced a third episode of epigastric discomfort and massive hematemesis with a fall in blood pressure to 60/0 mm Hg and a pulse of 126 per minute. The hematocrit was 30% and the hemoglobin 10.1 gm. A nasogastric tube was inserted and initially returned bright red blood, but within 30 minutes the return was clear. Over the subsequent 36 hours, five units of whole blood were given. After stabilization, exploration was performed.

At operation, the pancreas was found to be fibrotic. The head and body of the pancreas were enlarged sufficiently to create a pressure defect upon the stomach. The posterior wall of the stomach was densely adherent to the pancreas and peri-pancreatic tissue, but no pseudocyst was found. A duodenotomy was performed, and the duodenal mucosa was found to be normal. A long anterior gastrotomy failed to reveal any significant gastric mucosal abnormality, though the rugae were atrophic and there were several areas of mucosal erosion. The largest erosion was oversewn with silk and the gastrotomy closed. A truncal vagotomy was performed and the duodenotomy closed as a Judd pyloroplasty.

Postoperatively the patient did well until the 10th postoperative day when he experienced his fourth episode of massive hematemesis which failed to stop. After eight units of whole blood he underwent re-operation. The previous gastrotomy was re-opened and the point of bleeding was located on the posterior gastric wall high in the fundus. Bleeding was controlled by digital pressure. The adherence of the stomach to the pancreas necessitated a hemigastrectomy in order to expose the site of bleeding. The source of bleeding was a splenic artery aneurysm which had ruptured into the stomach. The splenic artery was ligated proximal to the aneurysm, splenectomy was performed, and the aneurysm resected (fig. 3). A gastro-jejunostomy and side-to-side jejunojejunostomy completed the procedure. Transfusion of an additional 12 units of whole blood was necessary during the operation.

Postoperatively the course was uneventful and the patient was discharged on the 36th hospital day.

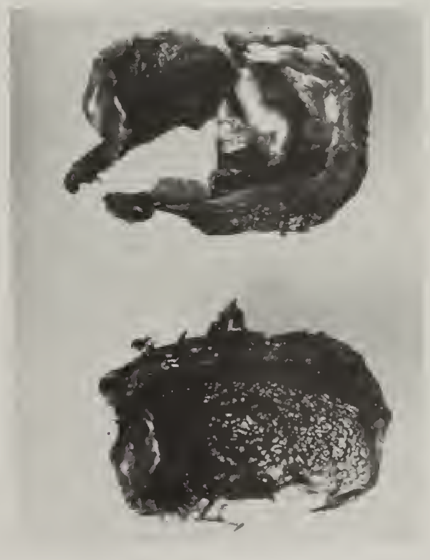

FIG. 3. Excised ruptured splenic artery aneurysm.

Discussion

Except for the aorta and iliac vessels, the splenic artery is the most common site of intra-abdominal aneurysms.[1] Symptomatic aneurysms of the splenic artery usually cause vague discomfort in the epigastrium, the left flank, or the left upper quadrant. Unless the aneurysm is calcified and therefore demonstrable radiographically, the correct diagnosis is seldom made pre-operatively. In the absence of calcification, arteriography will establish the diagnosis.

Between 35-45% of splenic artery aneurysms rupture, usually into the lesser omental space.[1,2] Since Bearessier's first description of a splenic artery aneurysm in 1770 more than 300 cases have been reported, but 14 cases of rupture of a splenic artery aneurysm into the stomach have been described.[1,3-6] Mortality from the rupture of a splenic artery aneurysm is reported to be 46% (76% if previously symptomatic).[1] If the diagnosis of splenic artery aneurysm is made pre-operatively, ligation of the splenic artery, resection of the aneurysm, and splenectomy are curative.

In the case presented, an interesting triad of symptoms was observed which might have suggested the diagnosis pre-operatively: sudden onset of mild epigastric discomfort, massive upper gastrointestinal hemorrhage followed by relief of the discomfort, and rapid cessation of the hemorrhage. Arteriography, if utilized, would have been diagnostic. It was contemplated in this patient only as a method to localize the site of active bleeding and was not performed when bleeding stopped so promptly on each occasion. However, vascular abnormalities are readily identifiable by arteriography. If the correct diagnosis had been suspected pre-operatively, arteriography would have led to the performance of the appropriate operative procedure at the first exploration.

In patients with massive upper gastrointestinal bleeding of obscure origin the possibility of rupture of a major vessel into an adjacent hollow viscus should be considered so that definitive diagnositic procedures will be performed.

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THE VIEW BOX

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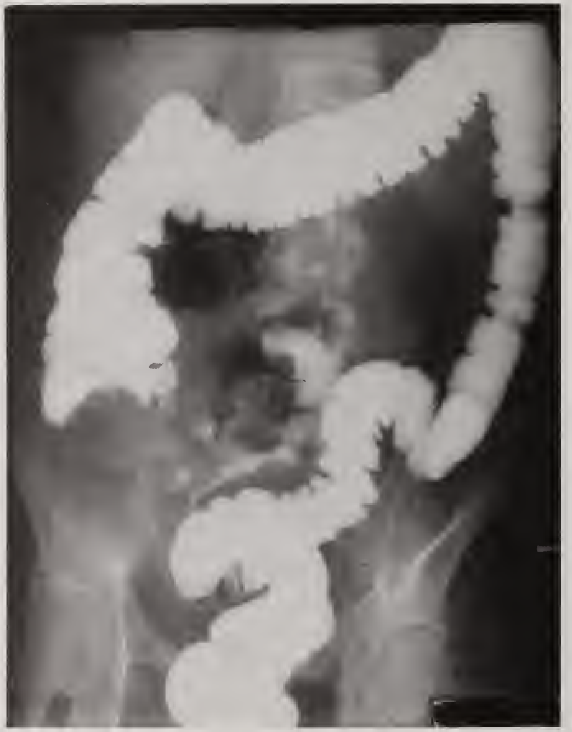

A 48 year old male was admitted to hospital with right lower quadrant abdominal pain. There was no change in bowel habits, no melena or weight loss. Physical examination revealed a 10 cm. mass in the right lower quadrant, partially moveable and tender. A Barium Enema examination was performed.

(for diagnosis see page 41)

Medroxyprogesterone Acetate (Provera^{R})[*] Therapy in Acromegaly Associated with Heart Disease[†]

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A 44-year-old acromegalic woman with congestive heart failure, conduction defect, and refractory ventricular arrhythmia was treated with medroxyprogesterone acetate (MPA) and estrogen in addition to Digoxin and conventional anti-arrhythmic agents. Growth hormone (HGH) levels decreased and symptoms improved, but the arrhythmia was unchanged and probably was responsible for her death. Autopsy showed massive cardiac hypertrophy with fibrosis of the myocardium and conduction system and a hypertrophied thymus gland. Acromegalics have a high incidence of conduction defects and arrhythmias which may prove resistant to conventional therapy or therapy with MPA and estrogens. MPA will decrease growth hormone in some but not all acromegalic patients and it may be useful in the setting of myocardial failure if this is in part related to the excess growth hormone.

Many patients with acromegaly develop cardiac insufficiency during the course of their disease, and often congestive heart failure and refractory arrhythmia are the causes of death.[1-5] Various modes of acromegalic therapy have been attempted, including megavoltage irradiation, proton beams, cryosurgery, ^{90}Y, and ^{198}Au implants. More recently medical therapy with medroxyprogesterone acetate (MPA) and chlorpromazine have been evaluated.[6,7]

The subject of this report is a patient with severe, untreated acromegaly who had cardiac decompensation, refractory arrhythmia, and conduction defects. Cardiac compensation was re-established with conventional therapy, but despite successful lowering of serum growth hormone (HGH) with MPA, the arrhythmia ultimately became refractory and the patient died suddenly in her sleep at home.

Report of Cases

E. R., a 44-year-old black woman first came to the WHC emergency room on May 3, 1971 with the chief complaint of sudden shortness of breath associated with headaches, nervousness, profuse sweating, and occasional arthralgias in her knees of many years' duration. Menses had ceased 20 years earlier after four successful pregnancies, and between the ages of 24 to 34 years old she noted an increase in the size of her face, hands, and feet associated with coarsening of her facial features. During the past 10 years no further change had occurred. She had been intermittently treated for 13 years for hypertension with butabarbital, reserpine, and hydrochlorthiazide.

In May 1968 at the age of 41 she was hospitalized because of traumatic shoulder pain and was noted to have a definite acromegalic appearance. There was no family history of diabetes mellitus or hypertension. Her four children were well. Physical examination revealed a blood pressure of 240/120 and grade 1 Keith-Wagner hypertensive changes in the ocular fundus. The heart was not enlarged. A grade 2/6 systolic murmur was heard over the pulmonic area. Chest X-ray films revealed a slightly increased left ventricular prominence. The sella turcica was described as being at the upper limits of normal size. The following normal values were obtained: serum calcium 4.2 meq/L; cholesterol 180 mg%; and 17 ketosteroids and 17-OH steroids 8.6 and 3.5 mg/24 hours respectively. The serum phosphorus was slightly elevated at 4.8 mg%. Glucose tolerance was normal. ECG showed right bundle-branch-block. The patient was referred to another institution in October 1968, where the following additional studies were obtained.

Visual fields were normal as was the intravenous pyelogram. T_4 was normal at 4.5 mcg; urinary VMA and catecholamines were normal at 5.3 mg and 40 mg at 24 hours. GTT was abnormal with a diabetic curve (table 1). Growth hormone levels could not be recovered from the records of this hospitalization, but the patient was thought to have inactive acromegaly, and no therapy was advised. She was lost to

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[*] Provera^{R}—Upjohn Company

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TABLE I: Glucose Tolerance Tests and Growth Hormone Determinations

Date	Fasting 30	30 min	60 min	90 min	120 min	180 min	240 min
5/68 GLU	92	169	184	–	113	71	71
10/68 GLU	106	170	188	192	153	106	
5/7/71 GLU	114	150	154		156	133	126
GH	19.4	20.0	30.0	–	18.6	15.8	20.0
+6/17/71 GLU	104	134	184		230	211	181
GH	not done	due to technical difficulties		–			
+10/27/71 GLU	118	177	222		250	185	102
GH	7.8	6.4	6.4	–	6.4	5.9	7.8

+On MPA 10 mg q 6h
GLU=Glucose in mg/100cc
GH=Growth Hormone in ng/ml (Double isotope method using the Schwartz-Mann Immuno Assay)

Hand Volume		Heel Pad Thickness	
7/14/71	750 cc	6/9/71	Right Pad=31 mm
8/25/71	725 cc	8/25/71	Right Pad-32 mm
9/20/71	725 cc		Left Pad=27 mm

follow-up for the following three years.

In early 1971 she noted the gradual onset of progressive shortness of breath with normal activity. One day prior to admission she developed orthopnea and was admitted the following evening in pulmonary edema. The blood pressure was 190/130, and the heart beats were irregular at 150/minute. Following treatment with rotating tourniquets, oxygen, diuretics, and digoxin, the pulmonary edema cleared but the arrhythmia persisted. The ECG showed ventricular bigeminy, left anterior superior hemiblock (LASH), and right bundle-branch-block (fig. 1). Chest X-ray films showed left ventricular enlargement with pulmonary edema (fig. 2). Bone X-ray films revealed cystic degeneration of the carpals, interphalangeal joints, and heads of the humeri (fig. 2). Morning serum cortisol was 31.7 mcg% (normal 7-27 mcg%), while pulmonary edema was present and 7.5 mcg% after congestive heart failure had cleared. GTT was abnormal, and growth hormone levels* were elevated in the basal state and non-suppressible following oral glucose (table 1). The patient was treated with several anti-arrhythmic drugs but continued to have a unifocal ventricular bigeminal rhythm. While maintained on digoxin 0.25 mg/day, therapy was begun with medroxypro-

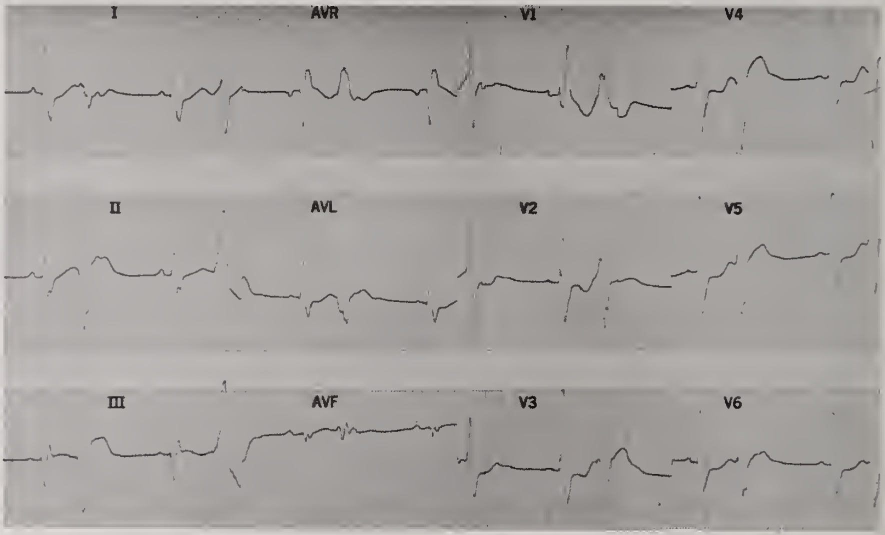

FIG. 1. Electrocardiogram from 6-16-71, patients's second hospitalization, illustrative of all tracings. It shows sinus rhythm with ventricular bigeminy, right bundle-branch-block with left-anterior superior hemiblock.

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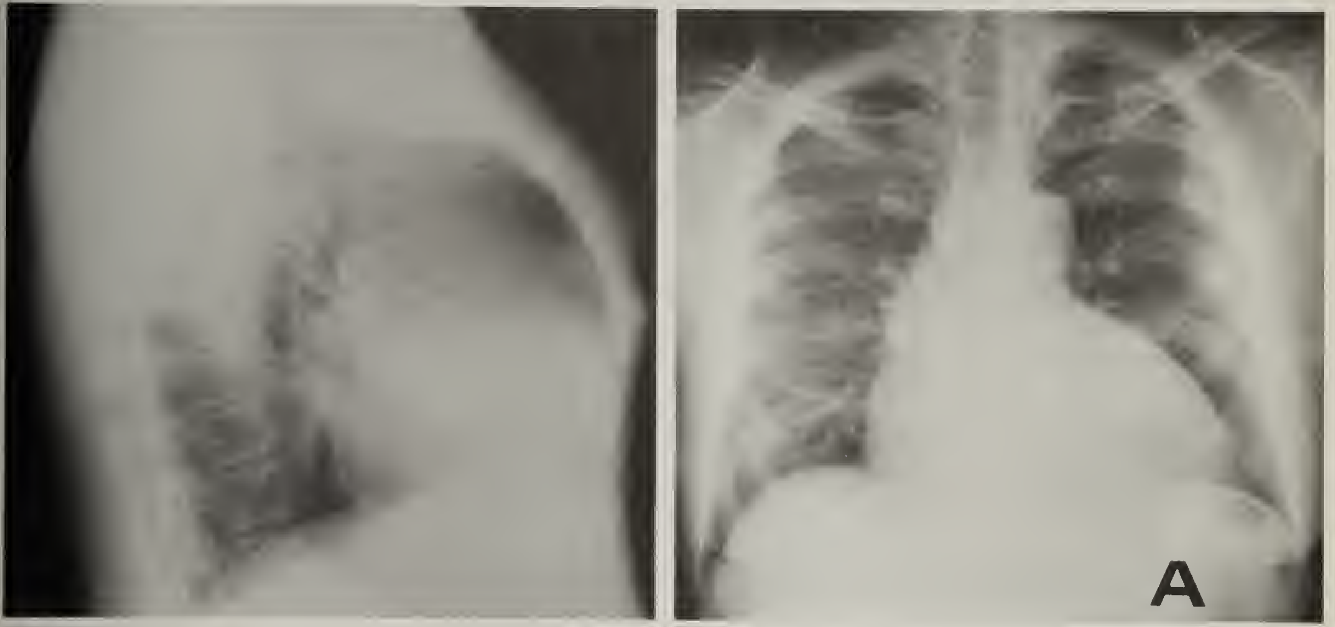
* Schwartz-Mann Immunoassay. Molinatti, G. M., et al: Radioimmunoassay of human growth hormone. J. Nucl. Biol. Med., 1969, 13, 26.



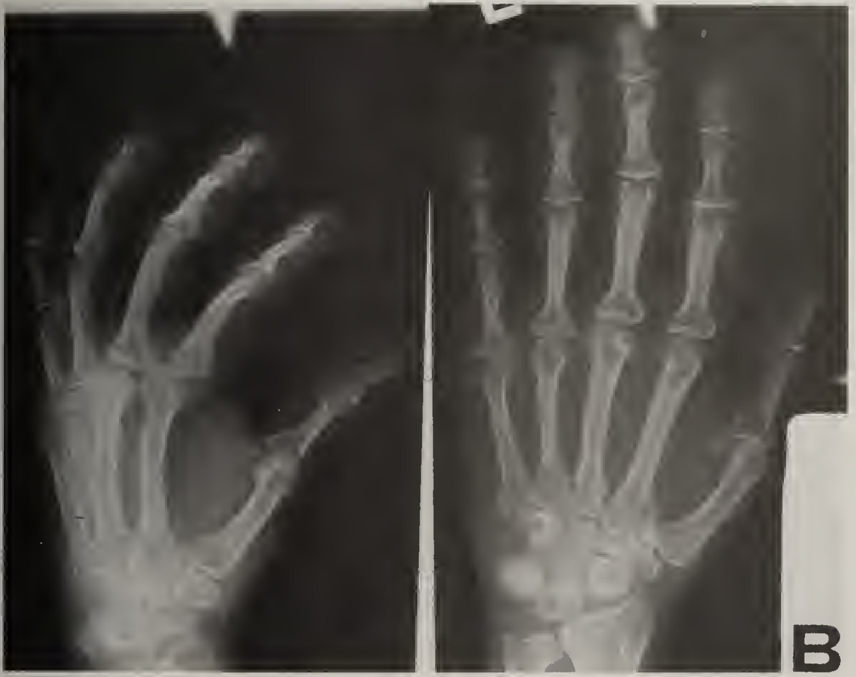


FIG. 2A. Chest X-ray films from first hospitalization, 5-10-71, showing bi-ventricular hypertrophy. (B) Hand films showing cystic degeneration of the carpals, metacarpals, and interphalangeal joints. This has been reported in acromegaly by Kjellgren.[13]

gesterone acetate 10 mg q 6h and an 1,800 calorie ADA, low-sodium diet.

Two weeks later the patient was re-admitted because of an increase in the number of premature ventricular contractions. She was asymptomatic. Procainaminde, 500 mg q 6h was added without much effect (table 2). With MPA continued, she was given conjugated equine estrogens, 15 mg/day IM, and then 10 mg/day orally in divided doses with no significant change in rhythm. No vaginal bleeding occurred.

The patient was discharged (June 26, 1971) on Digoxin 0.25 mg per day (later reduced to 0.125 mg/day, procainamide 500 mg every 6h, quinidine sulfate 200 mg q 6h MPA 10 mg q 6h, and conjugated equine estrogens 5 mg b.i.d. On July 28, 1971 an eight-hour Holter Monitor tape revealed no significant decrease in ventricular irritability, and the estrogen was discontinued (table 2).

Periodic glucose tolerance tests, growth hormone determinations, and eight hour Holter Monitor tapes were

TABLE 2: Results of Eight Hour Holter Monitor Tapes*

Date of Therapy	Premature Ventricular Beats/Normal Beats	%
5/22/71 Digoxin, MPA	1,400/25,500	5.5
6/18/71 Dig, MPA, Proc, Quinidine†	6,800/25,500	26.6
6/25/71 Dig. MPA, Proc, Quin, Prem	258/4,020	25.8
6/30/71 Dig. MPA, Proc, 432, Quin, Prem	6,355/32,636	19.4
7/26/71 Dig, MPA, Proc, Quin	6,874/30,128	22.2
10/27/71 Dig, MPA, Proc, Quin	5,411/30,502	17.7

* Technical difficulties causing less than 8-hour tape.

† Dig = Digoxin MPA = medroxyprogesterone acetate Proc = procainamide Quin = Quinidine sulfate Prem = brand name for conjugated equine estrogens–(Premarin®)——Premarin^{R}-Ayerst Co.

obtained over the next four months with the patient on the above regimen. A decrease in hand volume had occurred but heel pad thickness was unchanged. The patient noted a decrease in sweating and oiliness of her skin, decreased thickness of the soft tissue of her hands and feet and increased exercise tolerance. The cardiac arrhythmia and conduction defect did not improve. She died suddenly in her sleep at home on November 4, 1971.

At autopsy the heart (800 gm after embalming) was found to be massively hypertrophied and showed areas of fibrosis, within the muscle layers themselves, in the overlying endocardium, and in the right bundle-branch of the conduction system (fig. 3). The coronary arteries were normal, and the aorta showed only minimal atherosclerosis. The thymus weighed 50 gm and contained abundant lymphoid tissue (fig. 4). The thyroid was slightly enlarged but not hyperplastic. There was marked hyperostosis of the skull. The sella turcica was greatly enlarged with a downward herniation of the hypothalamic structures on top of a shrunken, collapsed pituitary. The pituitary showed extensive involutional changes in its central portion, with residual, active eosinophilic adenoma infiltrating the pia-arachnoid in the infero-medial surface of the apex of the left temporal lobe. The other endocrine organs were unremarkable.

Discussion

The patient was treated with MPA at a time when surgery was not feasible but prompt lowering of growth hormone levels was thought advisable. On MPA, the basal growth hormone levels declined (table 1). During a GTT four months after beginning MPA, the corresponding growth hormone levels were decreased relative to pre-treatment values, but the blood sugars remained in the diabetic range and the HGH was still non-suppressible by oral glucose. Conjugated equine estrogens given in an attempt to block peripheral HGH action were ineffective in reversing the refractory arrhythmia at a dosage of 10–15 mg/day.

Acromegalic heart disease remains controversial because of lack of agreement over whether growth hormone itself causes cardiac decompensation or whether associated hypertension, diabetes mellitus, or hyperthyroidism causes the cardiac failure. The high percentage of cardiovascular deaths in acromegaly (80%)[5] is much greater than the percentage of acromegalics with hypertension (19-33%), diabetes mellitus (10-25%). or hyperthyroidism (3%).[1–4, 8]

Growth hormone has been shown to increase protein synthesis in cardiac muscle cells of rats, resulting in hypertrophy.[9] The effect is independent of thyroid hormone, although thyroid hormone increases the response to growth hormone by increasing the work and force-producing ability of the heart.[10] Physiologically, with an uncontrolled, pathologic stimulus for hypertrophy, the contractile force eventually decreases, leading to myocardial insufficiency.[11,12] Similarly, growth-hormone stimulated-connective tissue hyperplasia might also contribute to the decreased myocardial contractility and conduction defects seen in acromegalics.[13] It may be that there is no single etiology for the cardiac insufficiency in the patient with acromegaly. Hypertension, or hyperthyroidism, or diabetes in any individual patient could potentiate the cardiomyopathy induced by the presence of excessive growth hormone.

The cardiomyopathy of acromegaly bears a striking resemblance to disease entities frequently grouped under the term "primary myocardial disease" or "idiopathic cardiomyopathy" IC[14,15]. In both IC and acromegaly the heart disease becomes clinically evident in the fifth decade.[14] The

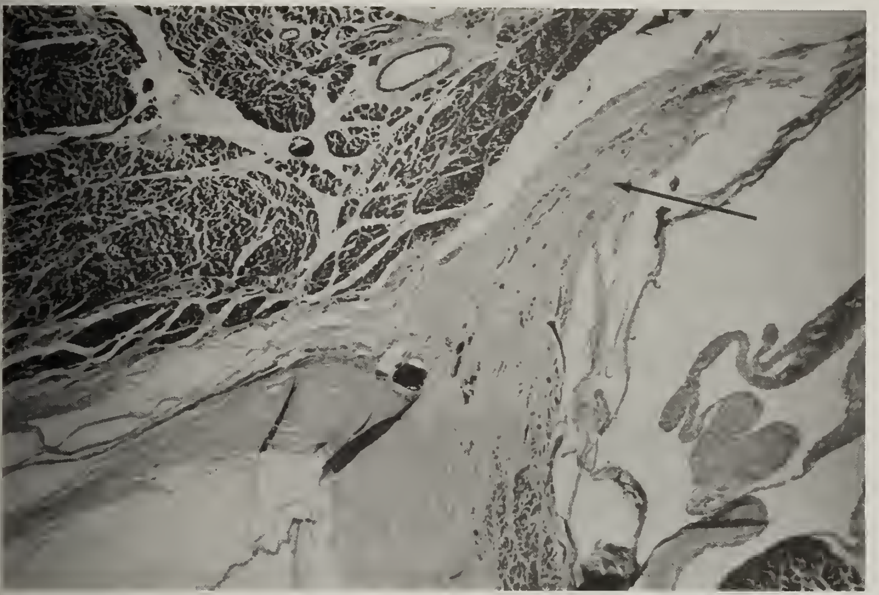


FIG. 3. Photomicrograph of bifurcation of bundle of His illustrating fibrosis of the right bundle-branch (arrow).

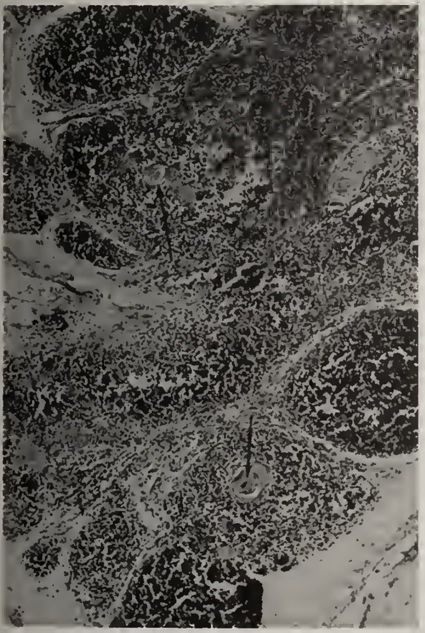


FIG. 4. Photomicrograph of thymus, including several Hassall's corpuscles (arrow), with surrounding lymphoid tissue.

symptoms are similar in acromegaly and IC with congestive heart failure predominating, with cardiomegaly often appearing years before the onset of the heart failure. Electrocardiographic abnormalities, especially ectopic premature ventricular beats, are common in both diseases, with PVC's noted in up to 43% of patients with IC.[1,3,14,16,17] Of the conduction defects seen in acromegaly, left bundle-branch-block predominates,[1,3] but occasionally isolated left axis deviation (LAD) has been found.[4] Other have found incomplete bundle-branch-blocks with QRS widening.[1] Our patient is an example of the less common right bundle-branch-block with left anterior superior hemiblock. The possibility of tri-fascicular block[18] with this type of conduction defect might suggest a cardiac pacemaker, but this was not used used because of the possibility of exacerbating the ventricular irritability.

The cardiac pathology in acromegaly is also similar to that found in IC with biventricular hypertrophy and an average weight of 500 gm or more.[15] The coronary arteries show mild, if any, atherosclerosis. Microscopic examination shows myocardial fiber enlargement with fibrosis.

Thymic enlargement as seen in our patient, has not been reported in IC. Thymic changes, however, with an increased number and size of Hassall's corpuscles have been reported in acromegaly,[19] and certain murine mammosomatotropic tumors have been shown to cause thymic enlargement.[20] The relationship between thymic hypertrophy and acromegaly is uncertain.

Our patient had a long history of mild to moderate hypertension which may have made her more susceptible to the cardiomyopathic effect of excess growth hormone. Treatment of the eosinophilic pituitary tumor itself has been shown to increase exercise tolerance and to decrease cardiomegaly.[11] We were unable, to find reports of improvement in cardiac rhythm or conduction defects following treatment. It may be that patients are seen too late in their disease when arrhythmias and conduction defects can no longer be changed with presenbly available therapy.

Medroxyprogesterone acetate[6,7,21-24] and estrogens[25,26] have been used to treat acromegaly with variable subjective and objective responses. Estrogens have been shown to transiently improve abnormal glucose tolerance in acromegaly due to its interference with the effect of growth hormone at its peripheral site of action.[25,26] The problems with estrogen therapy include short duration of action, danger of thromboembolic disease, feminization in males, menometrorrhagia, and carcinoma. Estrogen was used in our patient only to block any detrimental effect of elevated

HGH on myocardial rhythm and conduction but was not effective.

MPA probably acts at the level of the hypothalamus either by directly inhbiting HGH releasing factor or by non-specifically inhibiting the activity of several releasing factors.[6,7,27] Lawrence and associates[7] reported that 10 of 12 patients treated with MPA showed a substantial drop in HGH within six days. Three patients treated for three to nine months had subjective improvement with decreased arthralgias, myalgias, sweating, and headaches. Kolodny and co-workers[6] found a rapid response with both MPA and chlorpromazine in a short-term study. Conversely, both Atkinson and co-workers (23), and Malarkey and Daughaday[21] reported less favorable responses to MPA in acromegalics. The latter authors were unable to predict on the basis of an arginine infusion test which patients would respond favorably to MPA. Our patient did have a lowering of growth hormone while on MPA along with an improvement of some of her more subjective symptoms. She did not, however, show any improvement in her arrhythmia or conduction defect.

These conflicting reports illustrate the difficulty in evaluating any particular mode of therapy in acromegaly. Patients have shown dramatic improvement in spite of HGH values above normal.[23,24] No therapeutic regimen has been found to have 100% effectiveness in any large group of acromegalics nor to have an onset of action rapid enough to be efficacious in the setting of congestive heart failure with ventricular arrhythmia and conduction defect.[28-30] In our patient, X-ray therapy would have more gradually lowered growth hormone, but because of the arrhythmia, MPA was used to lower it rapidly. Since certain eosinophilic adenomas are under partial or complete hypothalamic control[31] other drugs acting at the hypothalmus may be found to be more consistently effective than MPA.

Acknowledgments

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Irving Burka, M.D.

The 106th President of the Medical Society of the District of Columbia, Dr. Irving Burka, assumed his new office on January 1, 1973.

Born in Poland, he has lived in the Washington area since his childhood. He received both his B.S. and M.D. degrees from the University of Maryland and took his postgraduate training at Sinai Hospital in Baltimore. He is presently engaged in the private practice of Internal Medicine at 4400 Connecticut Avenue, N.W. He is on the attending staff at George Washington University Hospital and the senior advisory staff at Washington Hospital Center.

Dr. Burka has been most active during his 35 years of membership in the Medical Society of the District of Columbia. His more recent achievements include the Society's Certificate of Meritorious Service, which he was awarded in 1966. He also served as First Vice President of the Medical Society in 1956. He was President-Elect during 1972.

Active in a number of professional organizations, Dr. Burka is a member of the American Medical Association, whose Physician's Recognition Award he received in 1969 and again in 1972; he is also a member of the National Peer Review Committee of the American Society of Internal Medicine. He was the President-Elect of the District of Columbia Society of Internal Medicine for 1971, and a past President of the Jacobi Medical Society, which organization named him its Man of the Year for 1970.

He is a Fellow of the American Geriatrics Society and of the American College of Angiology, and a member of the American College of Gastroenterology.

His concern with community affairs is reflected in his membership in the Metropolitan Washington Board of Trade and the Variety Club International. He is a past Vice President of the United Jewish Appeal of Metropolitan Washington and former Chairman of its Medical Division. He is also on the Board of Governors of the Anti-Defamation League of the D.C. and Maryland regions.

Dr. Burka is a member of the Adas Israel congregation and of the Woodmont Country Club. He is also President of the Metropolitan Washington University of Maryland Medical Alumni Association.

Dr. Burka is married to the former Rose Feldman. The Burkas, who reside in Chevy Chase, Maryland, have one daughter, Brenda, 30, two sons, Barrett, 33 and Steven, 22, and four grandchildren. In his leisure time Dr. Burka is a lover of music who enjoys the opera and the theater. He also has an interest in history and possesses a 20-year collection of American coins.

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medico-legal report

Liability for Transfusions of "Bad" Blood

A patient suffering from loss of blood is brought to a hospital where, shortly after arrival, he is given a transfusion. Three months later the patient contracts homologous serum hepatitis. He sues the hospital for damages.

This scenario is increasingly being played out in real life as the number of hepatitis-carrying transfusions—estimated now to be more than 30,000 each year, causing as many as 3,000 deaths—rises. In some recent cases the courts have granted patients large damage awards, overturning law that stood for many years. Thus, the law concerning accountability for "bad" blood is changing, so that physicians should be aware of the directions it may take and the precautions that may insulate them from liability.

Many mistakes may be made in giving blood transfusions, such as mislabeling blood, mismatching blood types or negligently performing the transfusion. Except to the extent that certain legal doctrines discussed below may excuse negligent acts, hospitals are liable for such acts. More careful selection, instruction and supervision of employees may prevent these mistakes. However, it is much more difficult to prevent patients from contracting diseases secondary to blood transfusions. In addition to hepatitis, diseases that may be transmitted by transfusion include malaria, syphillis, measles and influenza. Due to the relative ease with which the presence of these diseases in blood may be detected, it would appear that only the transmission of hepatitis should present a serious problem.

There apparently is no known method for removing homologous serum hepatitis from blood, nor is there any known means for detecting the virus in more than 25% of the cases of hepatitis-infected blood. The inability of most areas to obtain quantities of free volunteer blood (not donated for pay) sufficient to meet their needs has made it necessary for hospitals to use some paid-donor blood from commercial blood banks. Surveys indicate that blood from paid donors is far more likely (perhaps 50 or more times) to be hepatitis-infected than is free volunteer blood.

The necessity of using some paid-donor blood and the likelihood that it may carry hepatitis puts hospitals in a bind. Until recently, courts generally helped hospitals out of this bind when suit was brought against them, regardless of the theory of the suit (either negligence or products liability). A suit charging the hospital with negligence would have to show that the hospital or its employees either damaged the patient by improperly performing some function, or failed to perform some action they reasonably could have performed that might have prevented the patient from contracting hepatitis. Since the hospital could not stop using the hepatitis-carrying blood, nor could it have detected or removed the virus, the courts reasoned that the hospital could not be held to have been negligent.

In suits charging hospitals with selling a product (blood) that was unreasonably unsafe (because it carried the serum hepatitis virus), the courts formerly found that the hospitals were not liable. Most courts required there to have been a sale for the hospital to have been liable for having sold an unsafe product. Most courts followed a 1954 New York Court of Appeals ruling that a transfusion was not a sale of blood, but rather was a service performed by the hospital, in the course of which blood was transferred to the patient. This holding by the New York Court of Appeals has been reinforced by statutes in 23 states (including Virginia) that declare that transfusions are services and not sales. Nonetheless, the Supreme Court of Pennsylvania, in a 1970 decision reversing the dismissal of a damage action involving the death of a patient who had received a transfusion of hepatitis-infected blood, announced that it did not consider a finding that there had been a sale necessary to recovery for damage caused by the transfer of a bad product.

Another 1970 decision, *Cunningham* v. *MacNeal Memorial Hospital,* concerning a hospital's liability for the transfer of hepatitis-carrying blood, may have even more far-reaching implications. In the *Cunningham* case, the Illinois Supreme Court held that, regardless of the services rendered by the hospital in giving Mrs. Cunningham the transfusion and in performing numerous other related functions designed to improve her health, the transfusion was partially a sale of blood by the hospital. Although no charge for the blood was stated separately, the court concluded that the cost of the transfusion included a charge for the blood itself. After finding a sale, the court went on to consider whether the product was defective and whether the hospital was liable. The hospital had not informed Mrs. Cunningham of the possibility that a transfusion would result in her contracting hepatitis. While the Illinois court did not specifically rely on the non-disclosure, it seems to be implicit in the court's finding that the hospital had represented the blood sold as "good"—in other words, not carrying a risk of hepatitis infection. Thus, the blood sold was found to have differed from the product represented to Mrs. Cunningham.

Having found a sale of a defective product, the Illinois court still had to determine whether the hospital was liable. The major argument pressed by the hospital was that because there is no way to make blood safe from the risk of hepatitis, and because hospitals have to use blood, hepatitis-carrying blood is not *unreasonably* unsafe. Although no evidence was taken on this point, the court ruled that the possible absence of a means to ensure that blood used in transfusions did not contain homologous serum hepatitis virus did not protect the hospital from liability for its product.

If the *Cunningham* decision is followed, hospitals may be liable for damages whenever a patient contracts hepatitis within six months (the incubation time for homologous serum hepatitis) of his receiving a transfusion. However, two conclusions drawn by the Illinois court that are necessary to the finding of liability may allow other hospitals to avoid liability for damage from hepatitis-carrying transfusions. The first of these conclusions is that the hospital, by implication, represented the blood to be free of disease-causing virus. If hospitals use a written form clearly stating that the risk of hepatitis infection is involved in obtaining consent to the transfusion from the patient (or his representative), courts may find the transferred blood to be as represented, even if hepatitis results. While a form explicitly detailing the risk of infection might allow the hospital to avoid liability, a broadly-worded waiver of any recourse against the hospital for any infection or disease resulting from the transfusion would not be likely to do so because the bargaining positions of the hospital and the patient are inherently unequal. Furthermore, several questions with respect to a written consent immediately arise. For example: (1) Who will request the consent—the attending physician who orders the use of the blood and who may be required to share legal responsibility for its use, or the hospital? (2) Will a separate consent form be required for each unit of blood, or will all units administered by the hospital during a period of confinement be covered? (3) Will the consent form specifically state what tests for the detection of hepatitis-infected blood will be performed? (4) What will be the procedure for consent in those cases where the patient requires blood on an emergency basis and is perhaps unconscious?

The second conclusion on which the Cunningham decision rests is that the inability of hospitals to detect hepatitis virus in blood is irrelevant. The Illinois court in Cunningham relied heavily on the American Law Institute's second Restatement of the Law of Torts. The Restatement contains an exception to the general rule of liability for the transfer of unreasonably dangerous products that excuses transferors of products which are necessary but unavoidably unsafe. In essence, this exception allows a court to find that a product, though dangerous, is not unreasonably so because there is a great need for it and there is no known means for making it safe. Potentially hepatitis-carrying blood seems to fit within the category of products that are to some degree unavoidably unsafe.

At the same time, while all blood cannot be made safe from hepatitis virus, the danger of infection is not entirely unavoidable. If hos-

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pitals are to avoid liability by having the blood used in transfusions classed as unavoidably unsafe, hospitals should take whatever steps they can in order to make their product as safe as possible. At least three steps may be taken. First, to the extent practicable hospitals should avoid the use of paid-donor blood. Second, blood should be tested for homologous serum hepatitis virus; currently, testing for presence of the "Australia" (hepatitis-associated) antigen will detect the virus in about one-fourth of hepatitis-carrying blood.* Third, when it is possible to use plasma that has been stored at room temperature for six months, hospitals should do so; storing at room temperature can make plasma safe, although there apparently is no known method for making whole blood safe.

Even if hospitals fail to take these precautions that may prevent a finding of liability based on the Cunningham decision, they may still escape liability for transfusions of hepatitis-infected blood. To the extent they are recognized by state or federal law, two legal doctrines—charitable immunity and sovereign immunity—protect charitable institutions and governmental bodies, respectively, from liability for their acts. In Virginia, charitable hospitals are presently immune from liability for damage caused by the negligence of their employees, unless the hospitals failed to exercise ordinary care in selecting or retaining the employees at fault. No Virginia case has been found dealing with charitable immunity from liability for defective products. Maryland law provides that a hospital is not immune from liability, except that if the hospital has liability insurance for $100,000 or more, its liability for damage will be limited to its insurance coverage. Cases in both Virginia and Maryland have held that the state government cannot be required to pay for damages caused by its employees or institutions. These holdings may protect government-run hospitals, although courts in many parts of the country have become increasingly inclined to remove governmental immunity from liability. In the District of Columbia, neither sovereign immunity nor charitable immunity would eliminate or limit a hospital's liability.

Conclusion

Written consents to transfusions are recommended. Care should be exercised in securing such consents; they should disclose as completely as possible the risk of hepatitis infection. Further, hospitals should take precautions in procuring, testing and storing blood for transfusions in order to limit as much as possible the risk of transferring homologous serum hepatitis virus to the patient, as well as to limit the hospital's potential liability for hepatitis infection.

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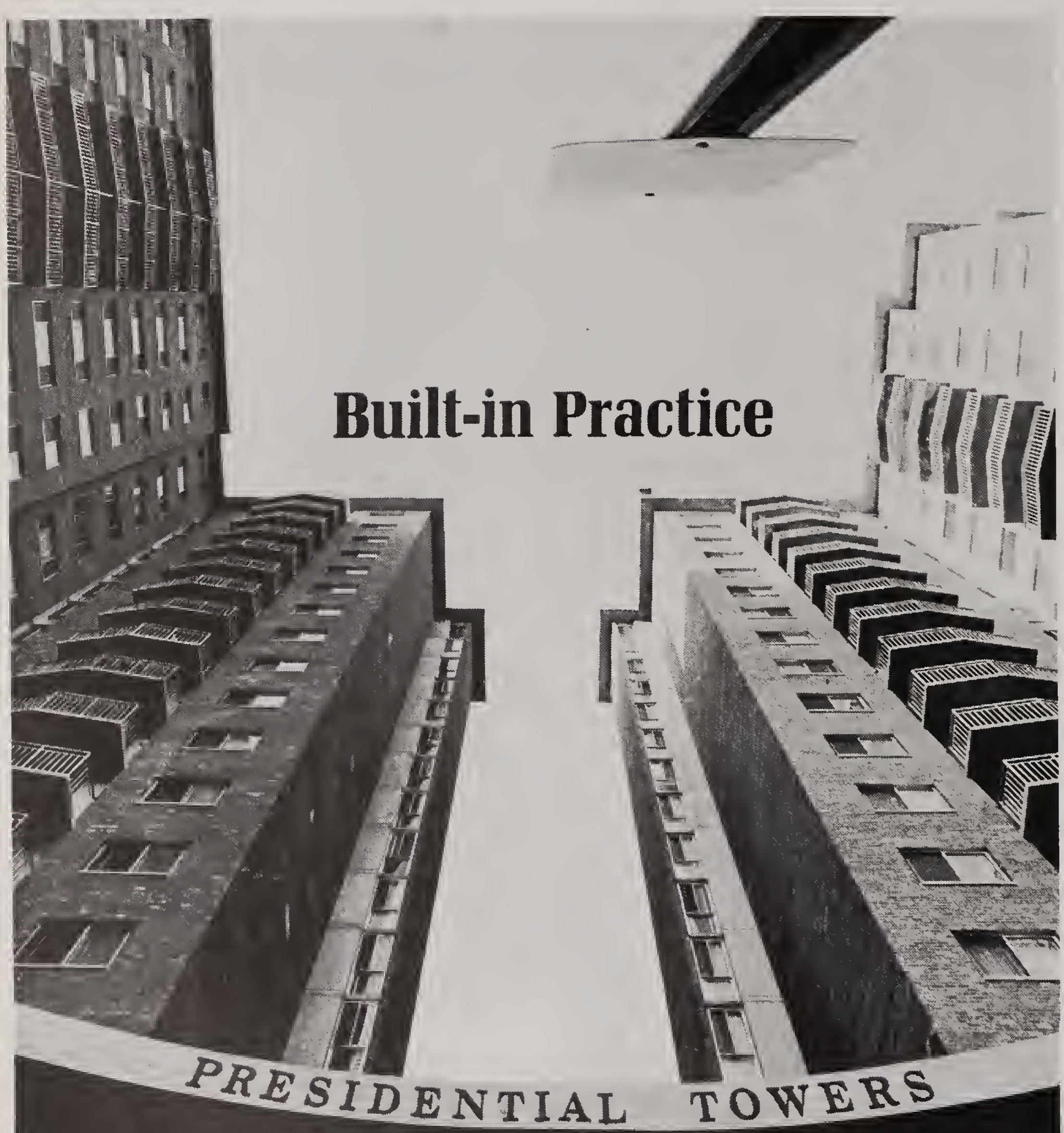
* It is expected that the use of the most sensitive testing modality known—radioimmunoassay—will at least double the present detection rate of "Australia" antigen. However, even this more sophisticated procedure will leave 50 per cent of all hepatitis-carrying blood undetected. Moreover, the equipment required to perform this procedure is quite expensive.



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Robert B. W. Smith, M.D., F.A.C.P.
Associate Editor
Medical Annals of the District of Columbia

The Executive Board of the Medical Society of the District of Columbia takes great pleasure in announcing the appointment of Dr. Robert B.W. Smith as Associate Editor of the MEDICAL ANNALS OF THE DISTRICT OF COLUMBIA effective January 1, 1973.

Born in Recife, Pernambuco, Brazil, he received his M.D. degree from Columbia University College of Physicians and Surgeons. He served his internship at Denver General Hospital and his residency at Walter Reed Army Hospital here.

Commissioned a First Lieutenant in the U.S. Air Force in 1949, Dr. Smith has had a most distinguished military career. He served as Chairman of the Department of Medicine at the Malcolm Grow U.S. Air Force Medical Center at Andrews Air Force Base here, and then as Deputy Director of Professional Services in the Office of the Surgeon General, U.S. Air Force. At the time of his retirement from the military in 1971 he held the rank of Colonel and the position of Chief Professional Consultant and Chief, Consultants Division, Office of the Surgeon General, U.S. Air Force.

He is currently an Assistant Clinical Professor of Medicine at George Washington University School of Medicine. He is also Senior Attending Physician at the Washington Hospital Center and on the attending staff at Doctors Hospital.

An active member of the Medical Society of the District of Columbia, Dr. Smith also holds membership in the American Medical Association, the American Thoracic Society, the Society of Air Force Physicians and the Association of Military Surgeons of the United States. He is a Fellow of the American College of Physicians, of which he served as Governor for the Air Force from 1968 to 1971, and he is also a Fellow in the American College of Chest Physicians.

Author of a number of scientific articles, Dr. Smith's literary talents are currently employed in the writing of a book on the ornithology of Japan. His interest in ornithology has led to the collection of a large ornithology library containing many rare volumes. He is in the process of building a weekend home/studio on Maryland's eastern shore, where he hopes to pursue a further interest in painting the birds of his studies.

He is married to the former Etsuko Yoshimura of Tokyo, Japan. They reside in Bethesda, Maryland with their four sons, John Rockwell, 19, Bruce Robert, 16, Peter Francis, 13, and Richard Warfield, 3. His leisure time pursuits also include duck hunting and photography.

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rtant Note. This drug is not a simple analgesic. Do
dminister casually. Carefully evaluate patients be-
starting treatment and keep them under close su-
sion. Obtain a detailed history, and complete
ical and laboratory examination (complete hemo-
, urinalysis, etc.) before prescribing and at fre-
t intervals thereafter. Carefully select patients,
ling those responsive to routine measures, contra-
ated patients or those who cannot be observed fre-
tly. Warn patients not to exceed recommended
ge. Short-term relief of severe symptoms with the
est possible dosage is the goal of therapy. Dosage
ld be taken with meals or a full glass of milk. Sub-
e alka capsules for tablets if dyspeptic symptoms
r. Patients should discontinue the drug and report
ediately any sign of: fever, sore throat, oral lesions
ptoms of blood dyscrasia); dyspepsia, epigastric
symptoms of anemia, black or tarry stools or other
ence of intestinal ulceration or hemorrhage, skin re-
ns, significant weight gain or edema. A one-week
period is adequate. Discontinue in the absence of a
rable response. Restrict treatment periods to one
in patients over sixty.
ations: Acute gouty arthritis, rheumatoid arthritis,
matoid spondylitis
raindications: Children 14 years or less; senile pa-
s; history or symptoms of G.I. inflammation or ul-
ion including severe, recurrent or persistent dys-
ia; history or presence of drug allergy; blood
rasias; renal, hepatic or cardiac dysfunction; hy-
ension; thyroid disease; systemic edema;
atitis and salivary gland enlargement due to the
; polymyalgia rheumatica and temporal arteritis;
nts receiving other potent chemotherapeutic
ts, or long-term anticoagulant therapy.
nings: Age, weight, dosage, duration of therapy, ex-
ce of concomitant diseases, and concurrent potent
otherapy affect incidence of toxic reactions. Care-
nstruct and observe the individual patient, espe-
the aging (forty years and over) who have
ased susceptibility to the toxicity of the drug. Use
st effective dosage. Weigh initially unpredictable
its against potential risk of severe, even fatal, re-
ns. The disease condition itself is unaltered by the
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including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement (B)98-146-070-G

Serious side effects do occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions.

For complete details, including dosage, please see full prescribing information.

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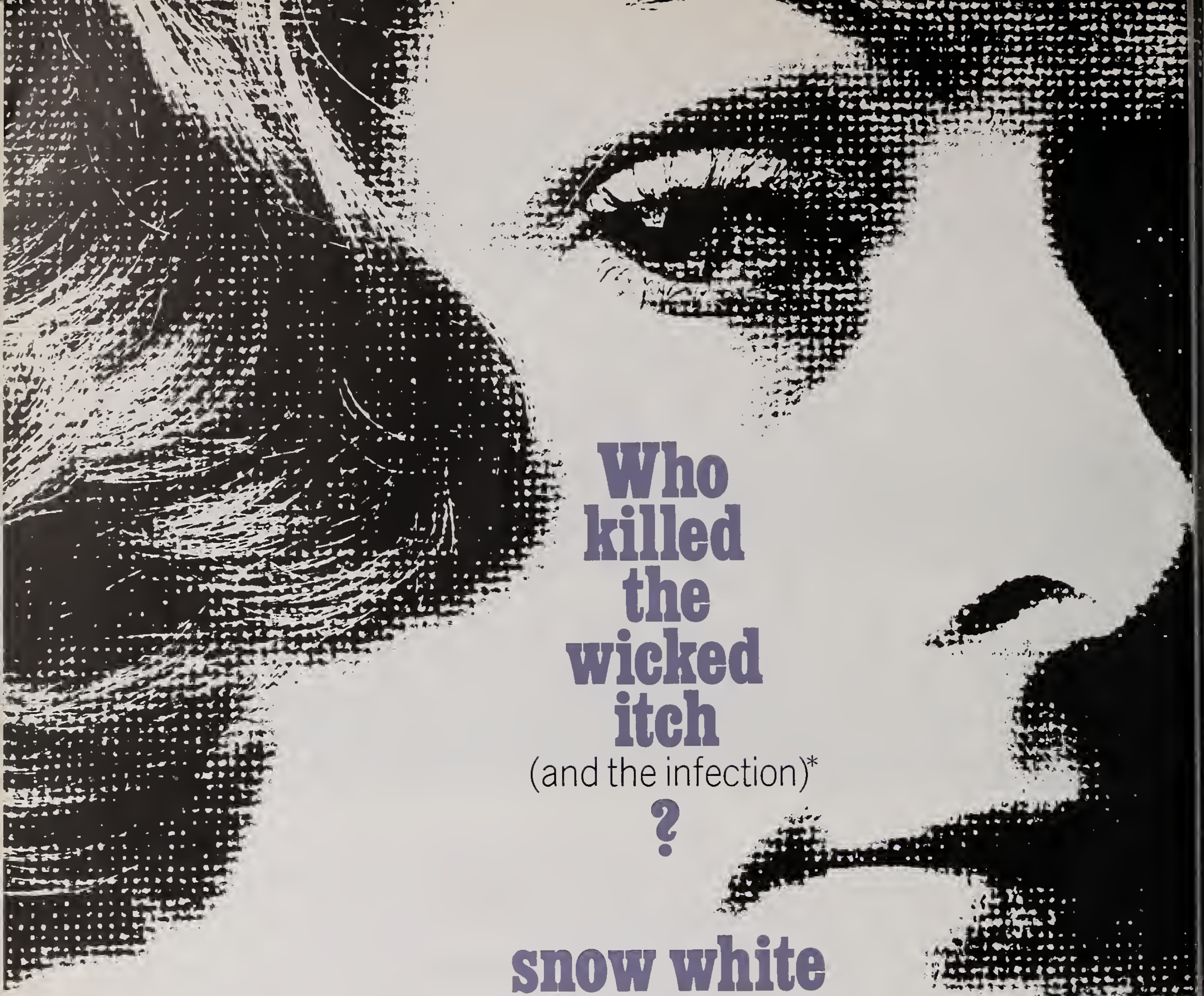

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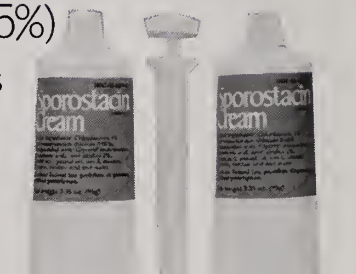

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: None known. **Precautions:** Cases of sensitization and irritation have been reported. When noted the drug should be discontinued. **Dosage:** One applicatorful intravaginally twice daily for a period of 14 days. Course of therapy may be repeated if necessary.

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book REVIEWS

In a Darkness. JAMES A. WECHSLER. Price, $5.95. Pp. 160. New York: W.W. Norton and Company, Inc., 1972.

In 1969, Michael Wechsler, a young man of twenty-six, after ten years of psychiatric treatment, killed himself by an overdose of sleeping pills. His father, James Wechsler, noted journalist and editorial page editor of the New York Post in collaboration with Michael's mother and sister, has written a personal history of his son's struggle with mental illness.

The story is told from the family's viewpoint; there are no contributions from the eight or more psychiatrists involved in the case and Michael's own feelings and thought processes are represented only by a few fragments of written material found among his effects.

It is not possible to know what impelled the Wechslers to construct this book. However, it would not appear that they were motivated solely by a desire to retaliate against the doctors whom they felt had failed them or to vindicate themselves from responsibility for the untimely death of their son. Rather it seems as if they were making an attempt to come to grips with the reality of their loss, to, as it were, relive in totality the experience so as to obtain some sort of intellectual closure or unburdening in order that they may in a sense free themselves from this most traumatic experience.

Whatever the impetus behind this particular book, the fact is that second to accidents, suicide is the leading cause of death among young people. Therefore an inquiry of this sort is of general rather than particular interest.

In the course of their narrative the Wechslers raise questions of the competency and adequacy of the psychiatric profession to deal with a case of this kind. In fact, in the body of the book, the quality of treatment provided to Michael medically after a near-fatal motor scooter accident is favorably compared with the treatment available to him psychiatrically in spite of the parents' willingness and ability to obtain for him the best care available.

The tone of the book is sweet reasonableness. These are people who are obviously used to working out their problems in a calm and rational fashion. They seem to feel that given a proper amount of concern and good will, most problems should lend themselves to sensible resolutions. It is a matter of shock and outrage that in spite of all that money, intention, and hard work could provide, they still lost their beloved and promising son.

Owing to the paucity of the material provided it is hard to review this book medically. It may be pointed out that the father, by virtue of his very virtues, brilliance, prominence, competence, rectitude, would most certainly present difficulties to a sensitive and delicate young man. However, if the narrative is to be trusted, and it has the ring of truth, there certainly was a considerable element of foul-up in the treatment the boy received.

For one thing, there were entirely too many therapists involved. Some of this can be traced to the fact that a change of residence took place, from New York to Harvard and back again. But there seemed to be entirely too little communication between the outpatient therapists and those at the residential facilities to which Michael was consigned. There would seem to be a good argument here for psychiatrists continuing to follow their patients when hospitalized as do internists and general practitioners rather than turning them over to a strange and autonomous unit.

Also the very crucial issue of communication between parents and psychiatrist is involved. When treating a young patient all psychiatrists have experienced the conflicting demands of the needs of the patient as opposed to the desire of the parents to be included and reassured. In some cases the progress of the patient is evaluated by the parents in terms of the degree to which the child conforms to their expectations. On the other hand, there is a tendency among certain psychiatrists to exclude the family to an almost ludicrous degree.

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The latter was the complaint of the Wechsler parents.

The narrative was fast-reading, touching, and compelling. Upon finishing this short book I had the feeling that I knew Michael and I felt some of his parents' tenderness toward him. Perhaps this was their intention.

ROBERT E. MORAN, JR., M.D.

Heart Block. RICHARD S. COSBY AND MICHAEL BILITCH. Price, $12.95. Pp. 251. New York: McGraw Hill Book Company, 1972.

This monograph sets out to assemble and digest the mass of information which has been accumulated in the last 15 or more years regarding normal and abnormal cardiac conduction and pacemaker therapy. It succeeds well enough to provide an extremely useful resource for those who require an overview of the subject. The bibliography of 245 references is well chosen and provides a starting point for more detailed research. The chapters devoted to the anatomy and the pathology of the conduction system are of particular interest to the clinician. In these chapters information heretofore scattered among a variety of sources is compiled in lucid style with adequate illustrations.

Those sections of the book devoted to electrophysiology and electrocardiography are regretably somewhat superficial. Greater detail concerning the most important advances in the understanding of A-V conduction of the past five years, namely the trifascicular block concept advanced by Rosenbaum and the contributions of His bundle electrography, would have been welcome.

The discussion of pacemaker therapy provides a sound approach to therapy based upon the authors' extensive experience. It tends, however, to be dogmatic. Many aspects of pacemaker therapy remain in dispute, e.g. pacemaker therapy in acute myocardial infarction. This observer would consider this monograph more valuable if it had indicated these areas of disagreement.

In summary medical students, house officers, and physicians who deal with pacemakers only infrequently will find this a valuable starting point for managing patients with heart block. For those who deal frequently with such problems its bibliography will be of considerable value as a point of departure in the search for more detailed information. Hospital libraries should obtain it.

JOSEPH LINDSAY, JR., M.D.

Clinical Concepts of Infectious Diseases. LEIGHTON E. CLUFF, M.D. AND JOSEPH E. JOHNSON, III, M.D., Editors. Price, $16.50. Pp. 421. Baltimore: The Williams and Wilkins Company, 1972.

This is a collection of essays by 20 authors who hope that the reader will obtain a perspective of the approaches important for thinking about problems in infectious diseases and caring for patients. There are five major sections, each with an introductory chapter by one of the editors. (1) "Mechanisms and Disorders of Resistance to Infections"—a somewhat brief description of the immune mechanisms. 2) "General Problems of Infectious Diseases"—a discussion of the clinical manifestations of infectious diseases. 3) "Specific Infectious Diseases"—twelve common infectious disease problems. 4) "Management and Prevention of Infectious Diseases." 5) "Tabulation and Other References of Infectious Diseases"—tabulation by syndromes and major manifestations.

Despite the numerous authors, the editors have achieved a concise and uniform approach to the diagnosis and treatment of infectious diseases which should prove to be of interest to students and practicing physicians alike. Many physicians will find the second and fourth sections particularly useful since they emphasize clinical management. For example, there are chapters on "Bacteremia and Bacteremic Shock," "Fever," and "Antimicrobial Therapy." There is an excellent chapter on "The Isolation of the Hospitalized Patient" which presents concepts developed at the National Center for Disease Control.

Although there are 12 chapters on common infectious disease problems, the editors refer the reader to the major textbooks of medicine for a compendium of esoteric infectious diseases. The authors have chosen, instead, to present a short readable basic approach to common infectious diseases.

JOHN C. PERKINS, M.D.

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The First Congress of the International Strabismological Association. PETER FELLS, M.A., M.B., D.O. Price, $29.50. Pp. 312 with illustrations. St. Louis: C. V. Mosby Company, 1971.

The first congress of the International Strabismological Association was held in Acapulco, Mexico on March 16 and 17, 1970. Forty-one opthalmologists from sixteen countries contributed twenty-one papers and participated in three symposia to promote, as Dr. Emma Limon de Brown, the chairman of the local organizing committee stated, "Mutual understanding in trying to deal with our common problems." This book is a complete compilation of what transpired in those two days.

Careful reading of the book leaves one with the impression that something less than mutual understanding was achieved and that mutual listening would have been a good beginning.

The opening symposium on "Early Operations for Strabismus" produced a useful classification of timing in strabisuus surgery by Dr. Arruga of Barcelona, Spain. His labeling of "prompt" surgery in regard to the onset of deviation is particularly apt. The disparity in viewpoint, methodology and goals was vividly represented by Dr. Parks who feels that a monofixation syndrome as the end result of treatment represents a therapeutic success, and Dr. Arruga who states: "fusion within ten diopters is precisely what we are trying to avoid."

The symposium on prisms emphasized the difference in philosophy between the old and new world. The European prismologists hospitalize their children for up to two weeks to receive prism therapy. Surgery is avoided or regarded as an adjunct to prism therapy. Anomalous retinal correspondence is the villain to be avoided at seemingly all costs and the child seems almost disregarded in the process. It remained for Mr. Kenneth Wybar, standing alone, to place prism therapy and orthoptic therapy in general in perspective.

Dr. vonNoorden's Bielschowsky lecture was an excellent compilation of current thoughts and experimental work on amblyopia. Several of the free papers were quite interesting. Dr. Chamberlain investigated the effect of one medial rectus recession for esotropia. Dr. Galin discussed the effects of diphenylhydantoin on the AC/A ratio, and Dr. Lang discussed his concepts of microtropia.

The practicing American ophthalmologist may want this book in his library to give him a wider perspective of the field of strabismus by including some points of view probably quite foreign to his own. Its absence on the shelf, though, would hardly be noticed.

THOMAS FREY, M.D.

THE VIEW BOX

(from page 16)

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Editied by Gunter J. Augustin, M.D.
Senior Attending Radiologist, Washington
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Drugs and the Public. NORMAN E. ZINBERG, M.D. AND JOHN A. ROBERTSON. Price, $2.95. Pp. 288. New York: Simon & Schuster, 1972.

Although the title suggests a review of drugs in general, in actuality only the so-called "drugs of abuse" are discussed, along with people's attitudes toward these drugs and their users, the supposed background for these attitudes, the Procrustean drug laws, and the pros and cons of various methods for dealing with such drug use. Discussion is also given to the British experience and the shortcomings of research on drugs.

The only background information given on the authors is on page 23 where it is stated, "One author is a psychiatric consultant on drug problems, the other a lawyer concerned with the impact of the drug laws."

With the notable exception of a description of projects funded by NIMH (pp. 99-113) and a listing of Zinberg's work (see footnote 3 on p. 269), most of the references cited (pp. 265-276) are not to scientific studies, but rather to "arm-chair" philosophizing, anecdotal and case history material, and other nonscientific material.

The authors have a fairly liberal view toward drug use. They wonder how Freud's "voice of intellect" can be heard, when emotion; lack of honesty, justice, and, hence, credibility; legal and public inflexibility; and puny efforts at research and medical and social care—rule the American climate. These criticisms apply especially to marihuana, with "probably over 20,000,000 users in the United States." A workable social consensus is hampered by public hysteria and especially the straitjacket of the law, which is somewhat overstated as the most important cause of crimes committed by and deaths from overdoses of addicts. Physician prescribing which fuels the seesaw of central nervous system stimulants and depressants, and the social demand for and free advertising of drug crutches and escapes adds to the whirlwind. As is well known, all research on

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marihuana was halted for more than 20 years when it became irrationally illegal. Only now are we establishing its limits of safety, and, indeed, efficacy as a medication. Research into roads to altered states of consciousness other than drugs is also proceeding. But how can you prescribe rational remedies and controls for an unknown entity?

The author's position and recommendations are given on page 259, entitled "A Licensing Model." They advocate "a system that permits drug use but does not encourage it, and that accepts restrictions based on age and on psychological or physiological incompatibility with the drug"; to them this would result in "the best balance of social and individual interests." Basically their licensing model would work the same way as the licensing of auto drivers (see pp. 260-261).

Chapter 1 discusses three types of drug users (pp. 12-13)–the personally and socially maladjusted, the "social" users (like the "social" drinkers), and drug-experimenters.

We think a more profitable way to look at this would be via a continuum of situationally-induced drug use vs. personality-induced use. This depiction would be congruent with most psychological theories which view behavior as a function of situational constraints and idiosyncratic components.

An example of a situationally-induced drug use would be one in which the environment is so horrible that drugs would be a rational means of coping with the situation. Maybe if the social milieu were more humane in its goals and activities, there would be less need for such drug use.

At the other extreme of the continuum (personality-induced) would be the person, who under the most beneficent of environments, would still have severe psychological problems.

The framework used by the authors for the study of drug use is functionalism; "the central orientation of functionalism is to interpret data by establishing the consequences of an action or situation for the larger structures with which it interacts" (p. 20). Such an approach would be expected from an author with a psychoanalytic background, since both psychoanalysis and functionalism are historic or genetic approaches. However, functional analysis is generally a *posteriori,* which makes it very easy, through the mechansim of hindsight, to explain anything.

The authors describe a series of studies (see "Sources of Information," p. 23) from which they state "much of the data and information on which we base our analysis of the drug situation was obtained." The interview method (*not* a well-controlled, blinded method) was used, and the 1161 subjects were from "all walks of life" and included Britishers as well as Americans. Nonusers and a potpourri of drug users, from marijuana to narcotics, were studied. The lack of using the scientific method allows the authors to attack but not disprove the drug domino theory. However, the results of the studies are scattered throughout the book, and very little of the book is devoted to presenting them.

In Chapter 2 the authors discuss three different attitudes that they feel represent the public's views on drugs:

(p. 37) "1. Drugs are all alike and all equally dangerous.

(p. 42) 2. Drugs are extremely powerful; they cause dependency which is physically destructive and leads to crime.

(p. 46) 3. Drug users are mentally ill."

Then they give reasons (i.e., the functions) why the public has the aforementioned attitudes. Also discussed is the public's treating of all drugs of abuse as equally bad.

Chapter 4 is one of the best chapters, since it collates and discusses the research (and accompanying results) funded by NIMH on: marijuana, hallucinogens, stimulants, narcotics, and sedative-hypnotics.

Chapter 5 compares the history and present state of British drug laws with American ones. The British model treating drug addiction as a medical problem is now being applied to alcohol in this country. Why not, as in Sweden, to other drugs? True, as the drug epidemic in Britain grew, physician prescribing and the medically unneeded supply had to be restricted, as the U. S. is attempting to do today. Both countries need to separate further the drugs of abuse on the basis of relative danger, to increase immeasurably the available medical care and social rehabilitation, and to eliminate Draconian punishment of supposedly monolithic evil in line with social realities.

Chapter 7 discusses the various aspects that should be considered when instituting or changing drug laws; e.g., effect on health of drug users; crime; obstacles to legal control;

costs to the legal system and society; manpower requirements; effect on the rule of law; civil liberties.

Chapter 8 discusses four essential features of any drug program: credibility, capacity for change, research and assessment, and provision of medical care. It also presents alternatives for present marijuana control and the authors' preferred solution: the previously discussed licensing model.

In conclusion, better presentations on drugs have been presented in *Psychology Today;* this publication has shown that scientific accuracy and good, interesting writing can be combined without sacrificing one to the other. Also the book relies heavily on the better documented 1970 book "Marihuana: The New Prohibition" by the Stanford expert, John Kaplan.

Well worth the price ($2.95), *Drugs and The Public* is recommended more for its stimulating message than for the validity of its findings. Hopefully, both the public and the Congress will consider the results of the badly needed, rapidly expanding, scientific research in the biological and social sciences to institute the rapid changes in attitude and acts necessary to humanize and revitalize American Society.

DEANNE KNAPP, PH.D.
ARTHUR RUSKIN, M.D.

Congenital Abnormalities in Infancy, 2nd Edition. A.P. NORMAN, Editor. Price, $22.75. Pp. 432 with illustrations. Oxford and Edinburgh: Blackwell Scientific Publications, 1971.

This book consists of 11 chapters by individual contributors, expert in their own fields, dealing with congenital malformations in infancy. The text is subdivided by organ systems, with an initial general chapter on etiology and incidence and two final chapters describing special syndromes and chromosomal anomalies. For the most part, chapter contributors are members of the staff of the Hospital for Sick Children at Great Ormand Street in London. The aim of the book is to describe the various anomalies recognizable in early infancy and suggest something about their management, including genetic counseling.

As usual with a book from England, the language is crisp and accurate. References are sparce and are gathered at the end of each chapter. One misses citations in the text when controversial points are made. Incidentally, this reviewer could not help noticing that initials are used for male authors, but complete names are written out whenever the author is a woman. For a book of this type, more emphasis than usual is given to management and less than perhaps is desirable to the embryology underlying particular conditions. The most serious defect is a lack of consistency between chapters. The chapter on central nervous system anomalies is well balanced, with appropriate emphasis on common problems such as meningomyelocele. The cardiovascular chapter spends too much time on physiology (a whole page dealing with the calculation of percent unsaturation) and therapy (detailed drug dosages and regimens for treating heart failure and arrhythmias) and even includes a section on interpretation of the electrocardiogram. The ENT chapter, in contrast, catalogues an infinite number of minutiae, devoting one paragraph to each.

Despite these defects, this book is interesting and should prove useful to those managing newborns with congenital anomalies. Its chief merit is the wisdom of the contributing authors, who tend to give their experience rather than to review the literature. One feels that he has made rounds at Great Ormand Street and learned at the bedside about various malformations. There is an agreeable flavour to this book, which contains, in addition, much useful information.

GORDON B. AVERY, M.D., PH.D.

Homeopathy in America. MARTIN KAUFMAN. Price, $10.00. Pp. 205. Baltimore: The Johns Hopkins Press, 1971.

Author Kaufman has carried out considerable and intensive research in assembling material for this book. He obtained data from many sources, including medical journals, the Frances Contivay Library at Harvard, Cambridge, the New York Public Library, the National Library of Medicine in Bethesda, Maryland, the American Medical Association and the American Foundation of Homeopathy, in addition to other sources of information to give an excellent account of the practice of homeopathy in the United States over a period of approximately one and one half centuries.

The book deals with the differences in the philosophy and therapy used by the orthodox

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or regular physicians, referred to all allopaths, as compared to those of various medical sects, more especially homeopathic or irregular physicians.

Orthodox medicine having as its beginnings such heroic practices as bleeding, cupping, purgery and drugs was in contrast to homeopathic medicine prescribing infinitesimal (diluted) doses of drugs which if given in large doses to healthy individuals would produce the same symptoms as the patient's disease. The practicing physicians of the former group were more progressive in seeking safer and more efficient methods and relied upon the body's natural healing processes and adapted to change in the use of their therapeutic modalities, while the homeopaths continued to adhere to their established principles of therapeutics and consequently became outdated. Thus as time went on the homeopathic adherents were not accepted in both private institutions and municipal hospitals and were not recognized by the orthodox physicians. The homeopaths were never able to gain acceptance as physicians to serve as medical officers in the armed forces.

The struggle against homeopathy was one of the many reasons for the formation of the American Medical Association. At the 1846 Convention it was resolved "That it is expedient for the Medical Association of the United States to institute a medical association for protection of their interests, for the maintenance of their knowledge and . . ." standard and improved requirements for the medical degree, that the student should possess a suitable education and that the entire profession should be governed by a code of ethics were considered. The code adopted in 1847 included the consultation clause asserting that "the good of the patient is the sole object of consultation between two or more physicians. No intelligent, licensed practitioner of good moral and professional standard should either be excluded from fellowship or his aid refused in consultation." It insisted that "no one can be considered as a regular practitioner or a fit associate in consultation whose practice is based on an exclusive dogma." No homeopath could consult with an orthodox physician. Thereby much bitterness evolved between the two groups within the medical profession.

In 1910 Dr. Abraham Flexner carried out an evaluation of the American medical colleges. Following his findings, passage of stricter medical licensing laws led to the collapse of the homeopathic schools since it became more difficult for them to meet the new standards.

This book is of value to the historian concerned with the development, the struggle and final outcome and failure of various medical sects in the United States during the years from approximately 1830 to almost 1970.

JOHN STUBENBORD, M.D.

Textbook of Electrocardiography. DAVID LITTMANN, M.D. Price, $22.50. Pp. 533 with illustrations. Hagerstown, Maryland: Harper & Row, 1972.

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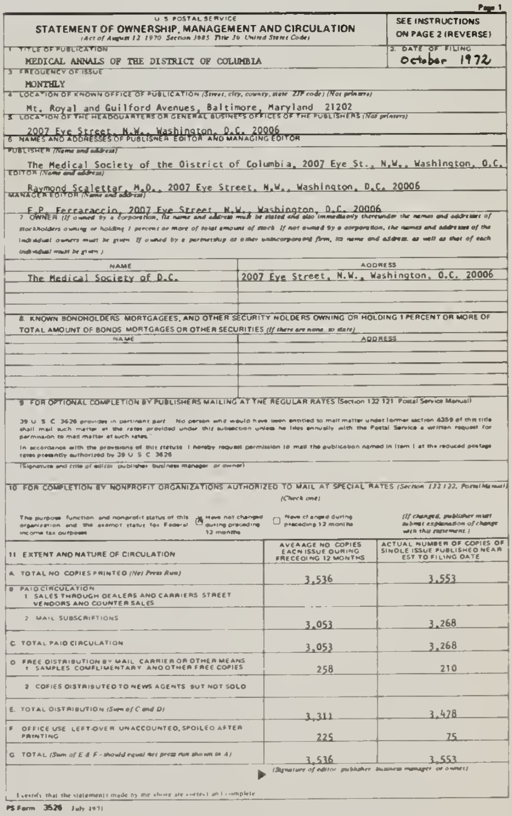

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- Burroughs Wellcome & Company 1
- Geigy Pharmaceuticals T-33
- Lederle Laboratories 4
- Eli Lilly & Company 8
- Ortho Pharmaceutical Corporation T-36
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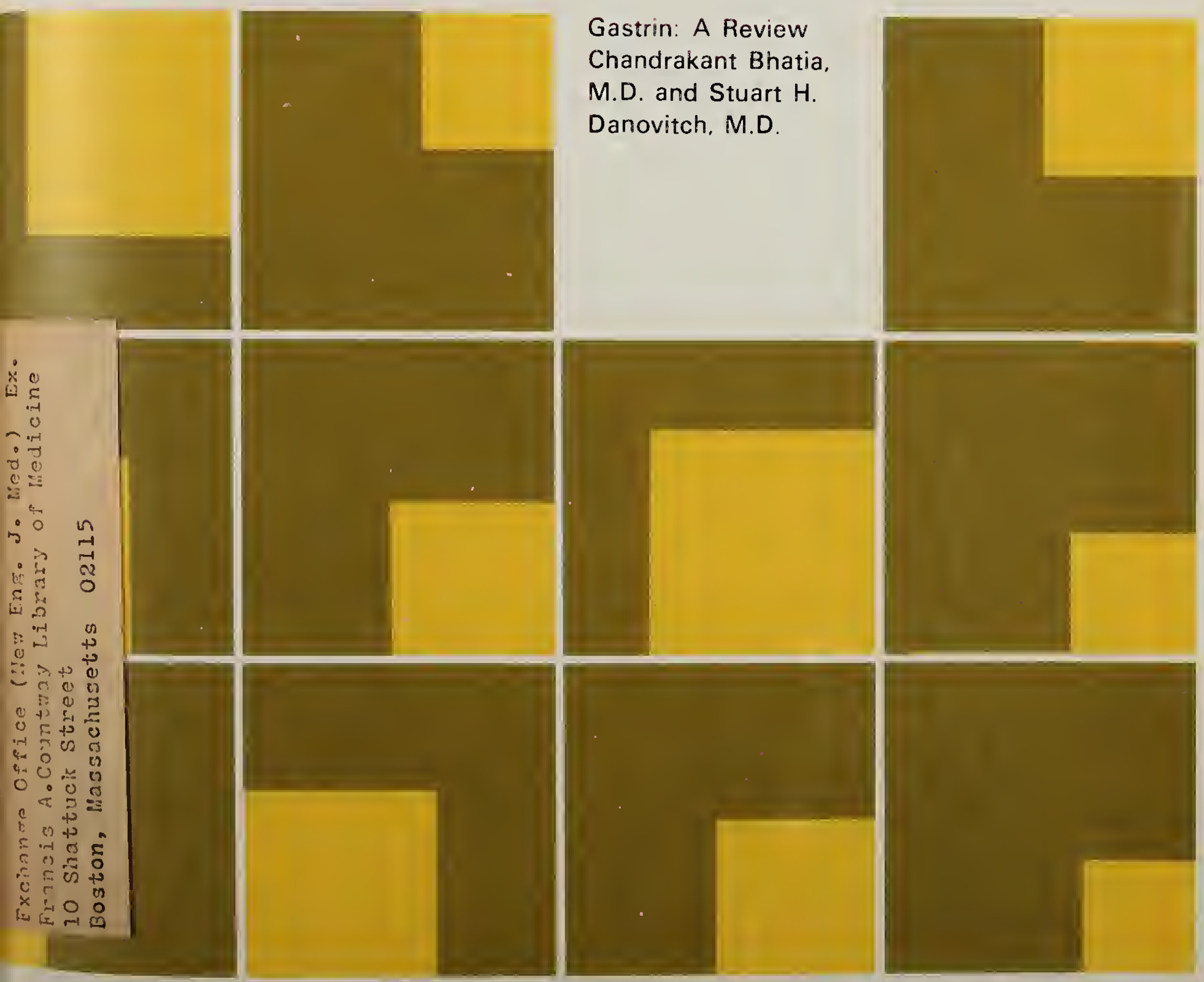

Gastrin: A Review
Chandrakant Bhatia,
M.D. and Stuart H.
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SCIENTIFIC ARTICLES

Gastrin: A Review. Chandrakant Bhatia, M.D. and Stuart H. Danovitch, M.D. . . . 51

Evidence of Chronopathology in Alcoholism. Ray B. Smith, Ph.D., Glenn Rowinski and Kathleen Kretzmer Gerstein . . . 55

Detection of Aspirin Sensitivity by Pulmonary Function Tests. Richard A. Nicklas, M.D. . . . 59

Psychiatric Aspects of Addison's Disease: Report of a Case. William F. Thompson, M.D. . . . 62

Unusual Metastases from a Transitional-Cell Carcinoma of the Renal Pelvis and Ureter. Willard A. Burns, M.D. and Attila T. Kadar, M.D. . . . 65

OTHER FEATURES

1973—Medical Society Committees 71

1972—Annual Business Meeting . . 77

Report of the Delegates to the AMA Clinical Convention. John J. Hughes, M.D. and C. Willard Camalier, Jr., M.D. . . . 85

The View Box . . . 86

Medico Legal Report. Surgeon's Liability for Nurse's Negligence—The "Lent Servant" . . . 97

New Members . . . 101

Book Reviews . . . 103
  Plastic and Reconstructive Surgery (May) Reviewed by Alfred J. Suraci, M.D.
  Medicine and Ethnology (Ackerknecht) Reviewed by Norman L. Wilson, M.D.
  Management and Treatment of Tropical Diseases (Maegraith and Gilles) Reviewed by George A. Tralka, M.D.
  An ABC of Medical Genetics (Carter) Reviewed by Steele F. Stewart, Jr., M.D.

(*continued*)

Wolff's Headache and Other Head Pain (Dalessio) Reviewed by Marvin C. Korengold, M.D.
Current Therapy—1972 (Conn) Reviewed by James E. Fitzgerald, M.D.
Early Care of the Injured Patient (Committee on Trauma, American College of Surgeons) Reviewed by Carlos A. Silva, M.D., F.A.C.S.
Practical Management of the Elderly (Anderson) Reviewed by Allan E. Lee, M.D.
Laboratory Tests in Diagnosis and Investigation of Endocrine Function (Escamilla) Reviewed by W. Tabb Moore, M.D.
Vectorcardiography in Congenital Heart Disease (Ellison and Restieaux) Reviewed by Antonio C. deLeon, M.D.
An ABC of Endocrinology (Catt) Reviewed by Max G. Sherer, M.D.

Obituaries ... 117

Classified Advertisements ... 13

Index of Advertisers ... 15

Information for Authors ... 16

Advertising and Subscription Information ... 16

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PRESIDENT'S MESSAGE

Irving Burka, M.D.

The AMA—Who Needs It? We Do!

As of now, and in the foreseeable future, I am convinced that every attempt will be made by some, in positions of power, to regiment, control, and diminish our rights and effectiveness as practicing physicians. We need unified strength, as well as increasing numbers of participating, active physicians to fight these battles.

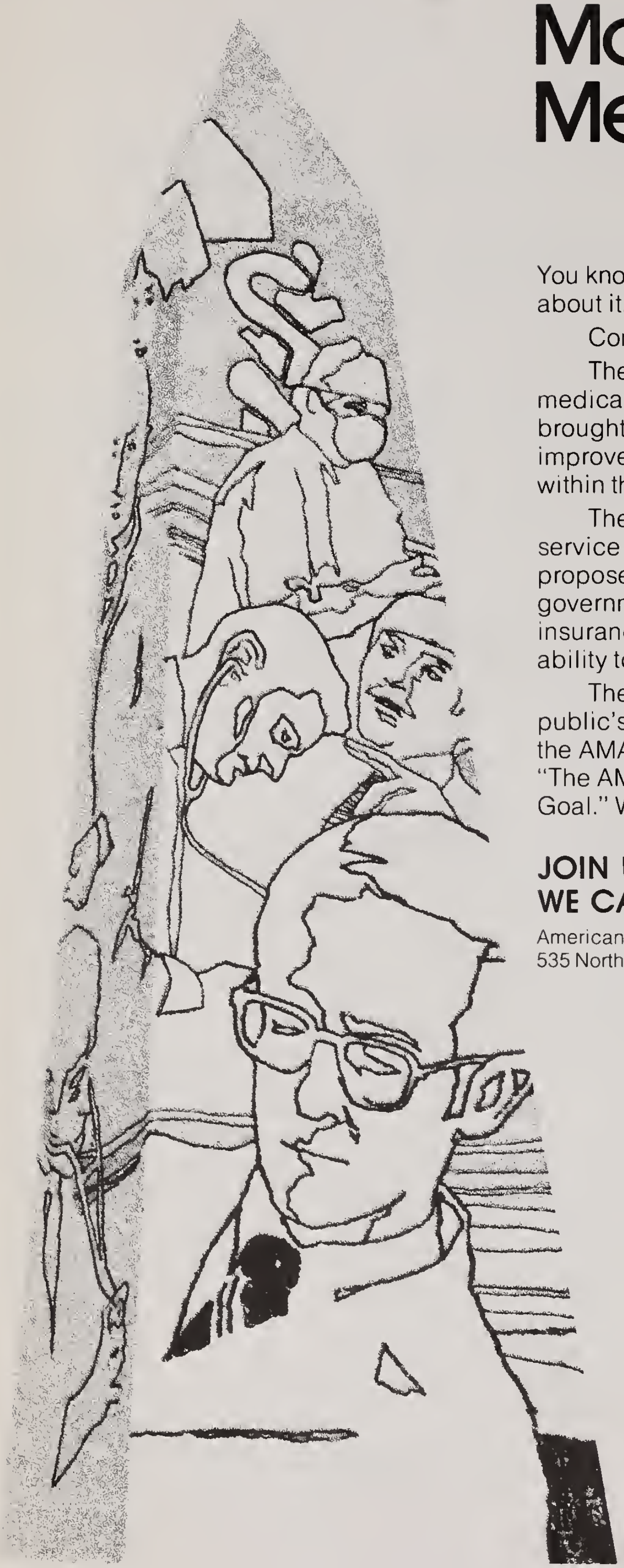
For over one hundred and fifty years, the AMA has been the spokesman for American medicine. At times it completely lost sight of its goals and certainly often has not been in tune with the wishes of the membership. I can personally remember during the Forties and Fifties, the strong feeling that I developed against the AMA, because I believed it had become an ultra conservative, unimaginative, obstructionist clique. I felt that it did not represent me. Today, however, we speak of a different breed, an entirely different AMA, a federation where membership is open to all ethical physicians. The membership also includes students, interns, and residents, who, incidentally are now eligible to serve in the House of Delegates, when duly elected.

The services offered by the Association are numerous and invaluable. The stress on Continuing Education, medical school accreditation, post-graduate accreditation for intern and resident training programs, investigations into the various means of provision for medical care, new drug investigations, peer review ethics, insurance programs, and many more projects, are well known to us. The total direction of all these services is to improve the lot of the physician and the quality of medicine for all of our people.

In the past many months, the Association has sent its Council on Long Range Planning and Development to many areas. This Council has listened to criticism, both constructive and otherwise, so that the opinions of County, State Societies, and also individual members might be considered. No more is it an Association representing a few. It can and will represent the majority thinking of American medicine, if given the chance.

There are those who feel that there are other groups, such as the AHA, splinter physician aggregates, and various speciality organizations that can and do represent the viewpoint and concensus of American medicine. I do not believe this to be true. The AMA is the only national medical organization where membership represents a cross section of all specialties, subspecialties, and various shades of political beliefs. It is, therefore, both by experience and diversification, the logical spokesman for all Medicine. By joining, we add to its strength, as well as recreating the Federation in our own image.

The AMA and organized medicine have become synonymous, and considered as such by both friend and foe. The opposite of organization is disorganization. It is to our advantage to keep it well organized.



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The AMA has vigorously opposed a government controlled medical system. And our testimony before Congress has brought results. Today key legislators acknowledge that improvement of health care can be best accomplished within the framework of our present system.

The AMA is acutely aware that more and better health service must be delivered to the public. To do it, the AMA has proposed a number of programs. One is Medicredit, a government supported program of voluntary national health insurance. It would insure every American—regardless of his ability to pay—of obtaining quality medical care.

The AMA is working hard to protect your interests and the public's. But we need your support. Find out more about what the AMA is doing for you and the public. Send for the pamphlet, "The AMA and the American Doctor: Sharing a Common Goal." Write: Dept. DW, at the address below.

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WE CAN DO MUCH MORE TOGETHER.

American Medical Association
535 North Dearborn Street/Chicago, Illinois 60610

Psychiatry: Fragmented Specialty?

Fifty years ago a physician, on being informed that his patient had seen a psychiatrist, had a rough idea of what was going on. In most instances he was reasonably certain that his patient had suffered a serious mental disorder and had probably been treated in a mental hospital–or "sanitarium," as it was then euphemistically called.

Twenty-five years later, that same physician could not be so certain. By that time, fortunately, it was perfectly "respectable" to consult a psychiatrist or psychoanalyst in his office. Psychotherapy for a wide variety of disorders, had become generally accepted.

In recent years, however, the statement by a patient, "I'm seeing a psychiatrist" conveys almost no idea of what is actually going on. Is he in individual therapy or group therapy? Is he in analysis? If so, which of several brands? Is he receiving chemotherapy or has he received Electroshock Therapy? Is he receiving supportive psychotherapy? Reality therapy? Behavior Therapy? Conditioning Therapy, family therapy, marital therapy, Primal Scream Therapy–or what?

If he's in group therapy, is he in an orthodox group, a nude-y group, or a feel-y group? Is it a weekend marathon group, a confrontation group, or a "T" group? Is he into Zen? Existentialism? Or Yoga?

What are the causes of such confusion and fragmentation? One could point to the complexity of psychiatry and the human condition, the imprecise nature of the healing process, the tensions of modern society, the over-tolerant attitude of American Psychiatry to unproven innovations, the enormous suggestibility of the emotionally unstable and the lonely–and many other areas. But one of the factors not sufficiently emphasized has been the tendency for a substantial segment of American Psychiatry to abandon the medical model. This is not to say that the psychiatric resident should not be familiar with the social, analytic and family interaction models. But each year the teaching of psychiatry in our medical schools seems to drift further and further away from the biological and clinical approaches to mental illness. The psychiatric resident may often know all about group dynamics but may not know how to cope with a disturbed patient. He may know the theoretical implications of the anal-erotic character but may be lost in prescribing an effective psychoactive drug for a seriously depressed patient. Such continued alienation from medicine places the whole future of psychiatry in jeopardy with respect to projected health care legislation. The psychiatrist of the future may be described by the bitter quip: "A person who practices psychotherapy without a Ph.D."

What is obviously needed in our medical schools is a return to the medical model with a greater emphasis on developing general psychiatrists who are trained to treat sick people. Such training must maintain a careful balance between the psychological and the biological roots of psychiatry. It must never be a question of "either-or." The modern psychiatrist must be well versed in both. Research is now giving growing support to the biological causes of mental disorders and this crucial area must never be neglected.

If general psychiatrists could be produced in sufficient number they could staff our community mental health centers, the psychiatric units of our general hospitals, and the consulting rooms of our country, thus reversing the trend away from the medical model. Conceivably, they might even help clear up the confusion about the current fragmentation of psychiatry.

Zigmond M. Lebensohn, M.D.

Anesthesiologists and Acupuncture

As is often the case with new drugs and new medical procedures, premature lay publicity gives rise to general public excitement and reaction.

This has been the case with the ancient Chinese art of acupuncture. This technique has a long history of practice in treating various ills of the Chinese people. Since 1955, it has been brought into Chinese hospitals where it has apparently been used as an anesthetic technique. It has been reported to have been used in approximately 20 per cent of the surgery in large Chinese cities with apparent success in the majority of such cases.

Responding to the American public clamor, the American Society of Anesthesiologists has moved in a responsible and commendable manner to indicate its interest and concern in studying and developing the technique.

Accordingly, the following news release was issued by the American Society of Anesthesiologists in June, 1972:

> The American Society of Anesthesiologists is gravely concerned over the premature application of acupuncture to American patients for relief of pain during surgery. The safety of American medicine has been built on the scientific evaluation of each technique before it becomes a widely accepted concept in medical practice. The premature use of acupuncture in the United States at this time departs from this traditional approach.
>
> A potentially valuable technique which has been developed over thousands of years in China is being hastily applied with little thought to safeguards or hazards. Among the potential hazards is the application to the patient who has not been properly evaluated psychologically. If acupuncture is applied indiscriminately, severe mental trauma could result in certain patients.
>
> Another hazard is the possible misuse by quacks in attempting to treat a variety of illnesses, including cancer and arthritis, thus diverting the patient from obtaining established medical therapy. Exploitation may delude the public into believing that acupuncture is good for whatever ails you.
>
> Acupuncture may indeed have considerable merit and may eventually find an important role in American medicine. That role can only be determined by objective evaluation over a period of years.
>
> As the discipline most seriously concerned, the ASA, whose membership is comprised of 11,500 physicians, feels a great responsibility to learn what it can through dialogue with Chinese acupuncture specialists. The value of acupuncture cannot be learned by a three-week junket to the People's Republic of China.
>
> The ASA believes that a team of American scientists, including anesthesiologists, neurophysiologists, psychiatrists, surgeons, and medical hypnotherapists should visit China under official auspices for an indeterminate period to give prolonged and serious study to acupuncture.
>
> The ASA has established its own task force to coordinate all activities concerned with acupuncture. It also has placed its resources and expertise at the disposal of the Federal Government in pursuing acupuncture studies.

M. L. B.

Utilization and Fee Review

It is evident that the public is deeply concerned with health care costs. The news media repeatedly decry the high cost of health care, both in the area of physicians' fees as well as hospital charges.

The continuing efforts on the part of the medical profession to maintain fees at reasonable levels has received scant attention in public statements. The diligent work of the Utilization and Fee Review Committees of our Medical Society should receive wider public knowledge.

Members of our own society may be unaware of the work of these committees. The Fee Review Committee meets monthly to review cases where the physician's fee is in question. Most of these cases are brought to the Committee by the insurance carriers, although physicians may initiate the fee review procedure if they are dissatisfied with a carrier's determination. Appeals may also be made directly by patients. The Committee is multi-specialty in composition and care is taken to have cases reviewed by peers in the physician's own specialty.

In the Metropolitan area, the insurance companies have accepted the recommendations of the Fee Review Committee of the Medical Society of D. C.

Similarly, the Utilization Committee decides cases that are referred from insurance carriers, patients, or physicians who feel a company has made an unjust determination of the utilization of services. These range from the number of times a laboratory test is performed on an outpatient to the length of a hospital stay for an in-hospital patient.

Whatever one's philosophical and emotional reaction to this type of review is, it is a fact of life and will continue to be so. These committees are composed of fellow members of the Society who try to be objective and fair. Two points deserve emphasis: (1) they serve as a buffer between the insurance company and the individual physician in adjudicating a problem case and (2) they serve as continuing evidence to the public that physicians can effectively review the practices of their colleagues.

Jerome Canter, M.D.

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> *"The history of science, and in particular the history of medicine . . . is . . . the history of man's reactions to the truth, the history of the gradual revelation of truth, the history of the gradual liberation of our minds from darkness and prejudice."*
>
> *—George Sarton, from "The History of Medicine Versus the History of Art"*

Are combination drug products useful in treatment involving concomitant use of two or more drugs?

Opinion

Results of a questionnaire to 7,000 physicians:

62.9%
Believe combination drug products are useful.

13.8%
Do not believe combination drug products are useful.

Are combination drug product
useful in treatment involvin
concomitant use of two or more drugs

Opinion & Dialogue

Doctor of Medicine

Louis Lasagna, M.D.
Professor and Chairman
Department of
Pharmacology & Toxicology
University of Rochester
School of Medicine
and Dentistry

Obviously, many drugs are given concomitantly. Whether it makes sense to combine medications in one preparation, be it capsule, tablet, or liquid, is a question that can be answered only by examining the advantages and disadvantages in the individual case.

Among the advantages is, first of all, convenience. The more medications that are taken concurrently and the more complicated the directions, the less likely the patient is to take medications accurately. From the standpoint of convenience and accuracy, and economy as well, you can make an important case for putting medications together in one preparation, as long as they are compatible.

By the same token, when you prescribe a properly tested and rational combination, you should have less worry about pharmaceutical or pharmacological compatibility – and about reasonable dosage ratios as well. Compatibility of the formulation should be demonstrated in the laboratory and clinic before the product is available for prescription—which is more than can usually be said for the physician's own spontaneous creations. And, the dosage ratios employed in rational precompounded combinations are designed to meet the needs of substantial numbers of "typical" patients.

There is no doubt that many "atypical" patients are to be found, and for them the prefabricated combination must be rejected. But that hardly argues for eliminating rational combinations from the market. Think, for example, of the problems that would arise if the components of widely accepted combinations, like the oral contraceptives and the diuretic-antihypertensives, always had to be prescribed, purchased and ingested separately.

One disadvantage that comes to mind is some doctors' unawareness of the ingredients a given combination contains. For example, a doctor might know that a patient is allergic to aspirin but forget that a certain analgesic mixture, which he knows only by its trade name, contains aspirin. His prescription, then, causes considerable discomfort, to say the least. This problem is a function of physician education, rather than of combination therapy as such. Improving doctors' knowledge about all medicaments they prescribe is a problem that deserves tackling on its own.

Another accusation leveled at combination drugs is that they encourage sloppiness of diagnosis and treatment. In many cases, however, a combination may prove to be the most effective choice. A good example of the usefulness of combinations appears in a recent article in the *Journal of Chronic Diseases* on the efficacy and side effects of an antihypertensive containing three ingredients, in which the track records of the combination drug and the individual ingredients were compared. Interestingly enough, whether the drugs were given individually or together, incidence and severity of side effects were the same. But blood pressure control was invariably better when the drugs were taken in one combination tablet than when they were taken separately (in "titratable" dosage) or in two or three different tablets.

Deciding which combinations constitute rational therapy obviously leads to a discussion of who is to determine which should be used and which should not. Realistically, I think combinations should be evaluated somewhat differently if they are old and established or new and untried.

In today's regulatory atmosphere, there is no possibility of a new combination being put on the market without a substantial amount of acceptable evidence in the form of controlled trials that show it to be safe and efficacious. On the other hand, I believe a different set of standards should apply to combination preparations that have been around for a long time. In other words, physician acceptance over a long period should be given some weight as evidence of the efficacy and safety of these drugs.

The FDA, however, does not seem to share this attitude. It often requires, for these older products, controlled trials that will monopolize the time of already overtired investigators and cost a greal d
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W. Clarke Wescoe, M.D.
President
Winthrop Laboratories

If two medications are used effectively to treat a certain condition, and it is known that they are compatible, it clearly is useful and convenient to provide them in one dosage form. It would make no sense, in fact it would be pedantic, to insist they always be prescribed separately. To avoid the appearance of pedantry, the "expert" decries the combination because it is a fixed dosage form. When the "expert" invokes the concept of fixed dosage form he obscures the fact that single-ingredient pharmaceutical preparations are also fixed dosage forms. By a singular semantic exercise he implies a pejorative meaning to the term "fixed dose" only when he uses it with respect to combinations. What is ignored is the simple fact that only in the rarest of circumstances does any physician attempt to titrate an exact therapeutic response in his patient. It is quite possible that some aches and pains will respond to 500 mg. of aspirin yet that fact does not militate against the *usual* dose being 650 mg.

The other semantic ploy often called into play is to describe a combination product as rational or irrational.

Take antibiotic mixtures, the source of much of the criticism generated against combinations generally. Obviously, no one should be exposed willy-nilly to the potential side effects of two or three antibiotics when only one is needed. At the same time there are cases where it is prudent to prescribe more than one. The clinician is the judge in these circumstances, as he should be.

There is no clear definition of the word rational. Most persons, I suppose, would find it synonymous with reasonable, but in many circumstances it may best be defined as the opinion of those in power at the moment.

Other factors govern combination therapy, not the least of which has been its broad use by practicing physicians anxious to achieve convenience in prescribing, to reduce medication error, and to save money for their patients. Combinations clearly have met the test on all three counts.

I have been impressed by studies showing that the rate of error climbs markedly with the number of medications to be taken, even with sophisticated patients. When medically justified, therefore, this factor alone supports the logic of combination therapy.

The cost argument for combinations appears to be irrefutable. In 1971, R. A. Gosselin studied the 71 combination products (excluding oral contraceptives) among the 200 most prescribed drugs. The study found that if all 71 products were discontinued, and if each ingredient in these combinations were prescribed separately, the price of medicines to patients would jump by $443.2 million on a national basis! At a time when the cost of medical care is under so much fire, it would be nonsensical to boost costs without clearly irrefutable medical reasons.

The part played by government on this question, of course, is fundamental. The FDA should play a role in determining which combinations are reasonable. That role, as defined by law and regulation, is to ensure that any medication on the market is safe and effective in line with its label claims. Certainly combinations are entitled to as much consideration as single entities—neither more nor less. So long as the addition of one drug to another does not make either less safe, or less effective, so long as they are compatible in a formulation, we have a reasonable product. It makes no sense to recommend the use of two products for certain conditions and to deny their being combined in a single form. An unhappy side effect of the problem concerns the efficacy panel discussions of many products submitted for review. The term "effective, but" has been freely interpreted to mean "ineffective" in toto, regardless of the merit of the individual drugs. This interpretation has placed numerous useful combination products in needless jeopardy.

In reading the actual reports of the review panels, it seems clear that some of the ratings were based less on scientific research and clinical observation than on the "informed" opinions of the panelists. These "informed" opinions were accepted at face value, while the "informed" opinions of others who had used the products were rejected. All of this put combination products into a sort of scientific never-never land.

It should be kept in mind by all, government as well as others involved in our health care system, that advances in therapy are seldom made in leaps and bounds but rather by small painstaking steps—and that some of these steps have resulted from research in combination drugs as well as with single entities. Given the near-infinite biologic variation in patient response, this is hardly surprising to clinicians. It should not be to regulatory agencies either.

In the end, the practicing physician is in the best position to decide if a particular combination makes sense. Such a decision should not be made exclusively by those whose responsibility for continuing clinical care is limited. Clinicians are the best judges of efficacy because the ultimate proof of any product's effectiveness is acceptance by physicians who have observed its actions in patients over time. The corollary statement may be made about over-the-counter medicines, which would not long survive if they failed to afford the relief the user anticipates. That the antihistamine in a "cold" remedy may not *always* be necessary is no reason to proscribe the combination generally.

Opinion & Dialogue

What is your opinion, doctor?
We would welcome your comments.

P·M·A

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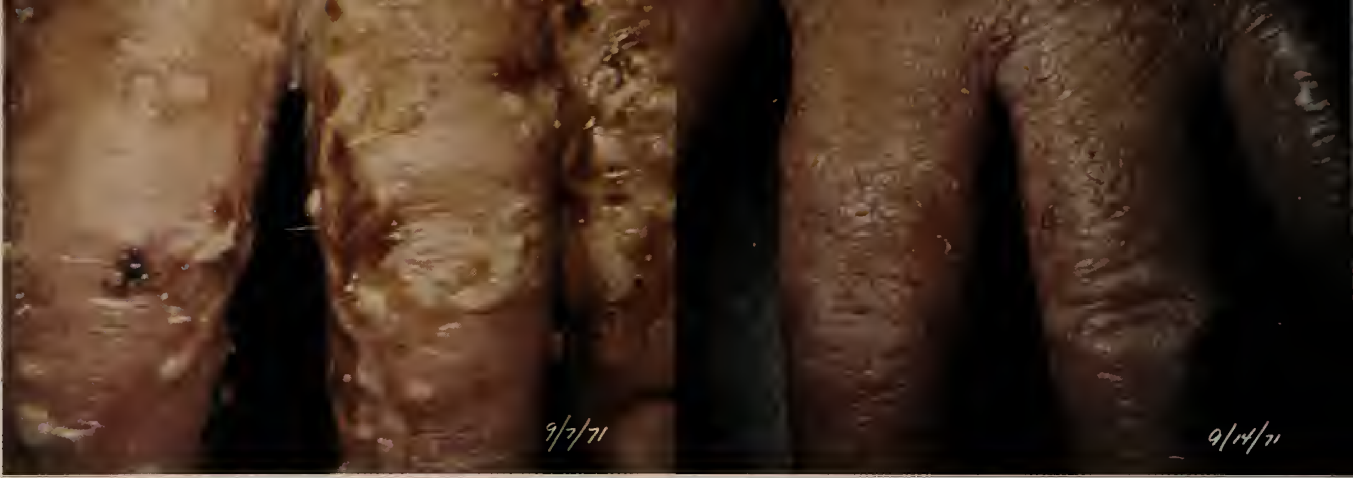

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Diagnosis: Severe pyoderma, left hand.
Culture: *Staphylococcus aureus, coagulase* positive and sensitive to MINOCIN.
Temperature: 102° F
Therapy: MINOCIN Minocycline HCl Capsules, 100 mg: 200 mg *stat,* 100 mg every 12 hours. Medication began 9/7/71. By fourth day, temperature was normal and pustular lesions considerably improved. Last dose taken 9/14/71.
Concomitant therapy: None.†

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Indications: For the treatment of susceptible infections; e.g., *E. coli, D. pneumoniae.* For full list of approved indications consult labeling.
Contraindications: Hypersensitivity to any tetracycline.
Warnings: The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This is more common during long-term use but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracyclines, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, use lower total doses, and, in prolonged therapy, determine serum levels. Photosensitivity manifested by an exaggerated sunburn reaction has also been observed in some individuals taking tetracyclines. Advise patients apt to be exposed to direct sunlight or ultraviolet light that such reaction can occur, and discontinue treatment at first evidence of skin erythema. Studies to date indicate that photosensitivity does not occur with MINOCIN Minocycline HCl. In patients with significantly impaired renal function, the antianabolic action of tetracycline may cause an increase in BUN, leading to azotemia, hyperphosphatemia, and acidosis. CNS side effects (lightheadedness, dizziness, vertigo) have been reported, may disappear during therapy, and always disappear rapidly when drug is discontinued. Caution patients who experience these symptoms about driving vehicles or using hazardous machinery while taking this drug. *Pregnancy:* In animal studies, tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Embryotoxicity has been noted in animals treated early in pregnancy. Safety of use during human pregnancy has not been established. *Newborns, infants and children:* All tetracyclines form a stable calcium complex in any bone-forming tissue. Prematures, given oral doses of 25 mg./kg. every 6 hours, demonstrated a decrease in fibula growth rate, reversible when drug was discontinued. Tetracyclines are present in the milk of lactating women who are taking a drug of this class.

Precautions: Use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, institute appropriate therapy. In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and blood serology repeated monthly for at least four months. Because tetracyclines have been shown to depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of such dosage. Test for organ system dysfunction (*e.g.,* renal, hepatic and hemopoietic) in long-term use. Treat all Group A beta hemolytic streptococcal infections for at least 10 days. Avoid giving tetracycline in conjunction with penicillin.

Adverse Reaction: GI: (with both oral and parenteral use): anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in anogenital region. *Skin:* maculopapular and erythematous rashes. Exfoliative dermatitis (uncommon). Photosensitivity is discussed above ("Warnings"). *Renal toxicity:* rise in BUN, dose-related (see "Warnings"). *Hypersensitivity reactions:* urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus. In young infants, bulging fontanels have been reported following full therapeutic dosage, disappearing rapidly when drug was discontinued. *Blood:* hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia. *CNS:* (see "Warnings.") When given in high doses, tetracyclines may produce brown-black microscopic discoloration of thyroid glands; no abnormalities of thyroid function studies are known to occur.

NOTE: Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption; do not give to patients taking oral minocycline. Studies to date indicate that absorption of MINOCIN is not notably influenced by foods and dairy products.

***Indicated in infections due to susceptible organisms. Culture and sensitivity testing recommended. Tetracyclines are not the drugs of choice in the treatment of any staphylococcal infection.**
†Case Report, Clinical Investigation Department, Lederle Laboratories.

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2. *Lactic Acidosis:* This drug is not recommended in the presence of azotemia or in any clinical situation that predisposes to sustained hypotension that could lead to lactic acidosis. To differentiate lactic acidosis from ketoacidosis, periodic determinations of ketones in the blood and urine should be made in diabetics previously stabilized on phenformin, or phenformin and insulin, who have become unstable. If electrolyte imbalance is suspected, periodic determinations should also be made of electrolytes, pH, and the lactate-pyruvate ratio. The drug should be withdrawn and insulin, when required, and other corrective measures instituted immediately upon the appearance of any metabolic acidosis.

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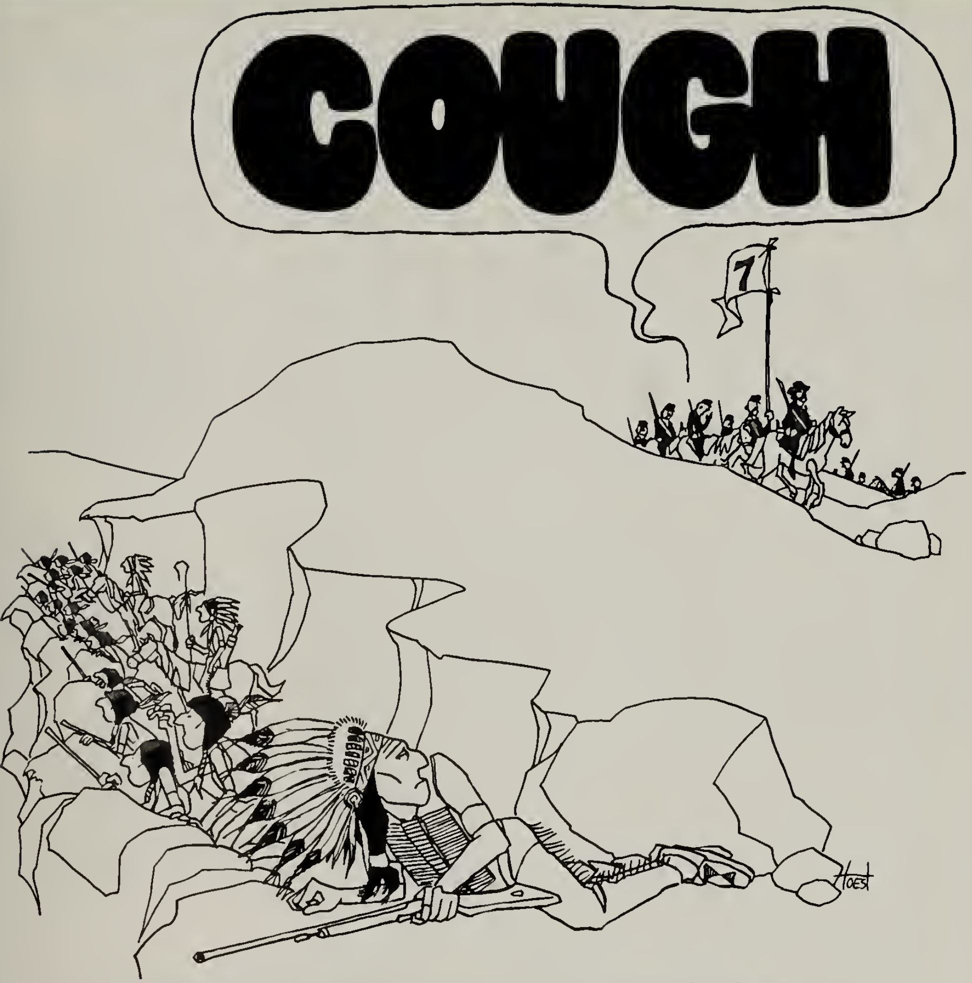
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Gastrin: A Review*

CHANDRAKANT BHATIA, M.D. AND STUART H. DANOVITCH, M.D.

In 1902 the discovery of secretin established the concept of "chemical messengers" which provided another means besides that of the nervous system for integration of bodily activities. This discovery also stimulated further investigation of hormonal mechanisms in the gastrointestinal tract which led to the elucidation of gastrin. Credit for these studies is due to John Sydney Edkins, a physiologist from St. Bartholomew's Hospital, London. In 1905, he published his work entitled "On the chemical mechanism for gastric secretion."[1] However this work was downplayed because of interest in histamine at that time; and the substance postulated by Edkins was thought to be none other than histamine itself.

The prevailing view that gastrin was, after all, histamine, was challenged by Simon Komarov,[2] who realized that if an antral hormone existed and was of protein nature, it would have been removed by deproteinization of crude antral extracts with which others had begun their search. Histamine would remain in the supernatant solution. Komarov precipitated protein from extracts of antral mucosa, and the histamine-free material stimulated gastric acid secretion. Activity was absent from fundic mucosal extracts, but scant amounts occurred in the proximal small intestine. This material appeared to be Edkins "gastrin". The first pure gastrin was extracted from pyloric antral mucosa of hogs by Prof. Gregory and Hilda Tracy in 1964, and was also synthesized by them in the same year.

Gastrin is a polypeptide with a molecular weight of 2114 containing 17 amino acid residues:

$$\text{Pyr-Gly-Pro-Try-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH}_2$$

Gastrin from antral mucosal extracts prepared from human, canine and sheep stomachs, contains 17 amino acid residues; differences among species are due to the substitution of one, or as in the case of sheep, two amino acids. In all species studied so far gastrin has been extracted in two forms—one containing a sulfate radical (called Gastrin II) on the tyrosine residue in position 12, and one lacking this residue (called Gastrin I). Its presence or absence does not appear to make a difference in the biological potency of gastrin. Thus the significance of these two gastrins is unknown, though one may represent a degraded form of the other.[3]

Biological activities of the full molecule are contained in the carboxyl-terminal tetrapeptide amide. Whereas loss of the penultimate aspartyl residue does not diminish the potency of the molecule, loss of the terminal amide renders it inactive. A synthetic pentapeptide possessing the carboxyl-terminal residues, known as pentagastrin, is commonly used for clinical and experimental purposes.[4,5]

Site of Production. The pyloric antrum is the main site of gastrin production. Other sites seem to include the pancreas and small intestine. The high concentrations of serum gastrin in the Zollinger-Ellison (Z-E) syndrome further implicate the pancreas as a site of gastrin production. However most pancreatic extracts, apart from the Z-E syndrome specimens, appear to lack gastrin-like activity. Immunofluorescent studies[6] have resolved the problem and have demonstrated gastrin in the delta cells of pancreatic islets. The small bowel gastrin may mediate the "intestinal" phase of gastric secretion occurring when partially digested food enters the duodenum.

Mechanisms of Gastrin Release. Numerous chemicals are potent stimulants to gastrin release, particularly meat and its component proteins and polypeptides. Ethyl alcohol is also a strong stimulus for gastrin release, providing a physiologic basis for its proscription when minimal stimulation of gastric acid is desired.

In addition to ethanol, propyl alcohol, glycine and β-alanine are effective stimulants as well. Whereas dipeptides like glycyl-glycine release gastrin, the tripeptide is totally ineffective in this regard. Thus the receptor site in the antrum possesses certain conformational characteristics.

In addition to the above dietary chemical stimulants, certain pharmacologic agents have the capacity to release gastrin. Application of a 0.1-1% solution of acetylcholine chloride to antral mucosa is a more potent gastrin releaser than either amino acids, peptides or alcohol. Experimental studies suggest that parasympathomimetic drugs directly stimulate gastrin producing cells, since topical atropine abolishes gastrin release not only following this stimulus, but all others as well. However, systemically administered atropine does not inhibit the release of immunoassayable gastrin in response to feeding in man.[7] Bile salts are also known to affect release of gastrin, since exclusion of bile from the gastrointestinal tract diminished the intestinal phase of gastric secretion. Presumably bile salts or some other component of bile facilitates the release of a hormonal agent from the small intestine responsible for gastric acid stimulation. Perhaps it is the pH of bile which is important, since raising intragastric pH above 3.0-3.5 enhances gastrin output, whereas a fall in pH below this level exerts a negative feedback control on gastrin synthesis and/or release, thus providing a brake on persistent hydrogen ion secretion by the stomach.

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Mechanical stimuli, as well as chemical, release gastrin. Antral distension is important in this regard. The mechanical pressure required to cause release of gastrin is quite small and well within the physiologic limits encountered after ingestion of a meal. Mechanical pressure may act directly on gastrin containing cells or work through a short intramural cholinergic reflex arc.

Nervous impulses provide still another control of gastrin secretion. Psychological stimuli transmitted via the vagus to the pyloric antrum cause gastrin release. Additionally intact vagal innervation seems to maximize the acid secretory response of both chemical and mechanical stimulation of antral mucosa.

Physiologic Effects of Gastrin. Prior to its purification and subsequent physiologic testing, gastrin effects were thought to be confined to that of stimulation of gastric acid secretion. It is now clear that pure gastrin, or its active terminal tetrapeptide amide, possess other properties. As noted gastrin is a potent stimulant of gastric acid secretion, approximately 500 times that of histamine on a molar basis. However, intravenous injection of gastrin in large doses may inhibit gastric secretion, at least in the dog and rat. Hence it is easy to see how this anomalous behavior may have led previous investigators to believe that their antral preparations were inactive. Paradoxically, the very large doses of gastrin that inhibit acid secretion in dogs will still cause marked stimulation of pepsin secretion.

Gastrin also has an abiding effect on gastrointestinal motility. It causes contraction of gastric and small bowel smooth muscle in dogs. From such studies Bennett has concluded that gastrin liberates acetylcholine from nerve teminals in the tissue.[8] Recent studies demonstrate the important role of this hormone in regulation of lower esophageal sphincter (LES) pressure. Castell and Harris[9] have demonstrated a marked increase in gastroesophageal sphincter strength following alkalinization of the stomach. Pentagastrin administration mimicked this effect on LES tone, which could not be attributed to concomitant acid secretion since instillation of 0.1 N HCl into the stomach decreased LES pressure. Abolition of 80% of resting LES pressure by administration of antibodies to gastrin to experimental animals, demonstrates the primacy of this hormone in the genesis of LES pressure. Patients suffering from peptic esophagitis have a diminished LES pressure. Whether their circulating plasma gastrin concentrations are diminished or whether their sphincter responds inadequately to normal concentrations is unknown. However alkalinization of the stomach, which stimulates endogenous gastrin release, seems to restore LES tone toward normal in such patients. Obversely patients with achalasia have a hypertensive LES which is suprasensitive to circulating gastrin.

Gastrin also effects the pancreas and liver, weakly stimulating water and bicarbonate output by these organs. This effect provides a rationale for gastric decompression when complete rest of the pancreas is desired, as in acute pancreatitis.

Gastrin also stimulates intrinsic factor secretion by human stomach. Conflicting reports exist about effects of gastrin on the circulatory system. Collapse and a peculiar "sinking" sensation have also been described in man following large intravenous doses of gastrin.[10]

Measurement. In 1968, McGuigan and Trudeau[6] described a radioimmunoassay for gastrin measurement. Early efforts to produce antibodies by immunizing rabbits with pure porcine gastrin, were unsuccessful, as were efforts to elicit antibodies with gastrin specifically using the C-terminal tetrapeptide amide (Try-Met-Asp-Phe-NH_2) attached to a carrier protein to facilitate immunogenicity. Currently covalent conjugation of human gastrin I, residues 2-17 to carrier macromolecules, viz. bovine serum albumin, and injection into rabbits yields antibodies that are sufficiently sensitive and specific, do not react with pancreozymin cholecystokinin which possesses the same C-terminus, and allow the measurement of gastrin in human blood. Conjugation of these antibodies to fluorescein has led to identification of the "gastrin cell" in antral mucosa. Both human and porcine gastrin are localized in or on granules in the cytoplasm of differentiated epithelial cells interspersed along the course of antral pyloric mucosal glands. Gastrin activity seems confined mainly to the middle third of the antrum by this method.

Mechanisms of Action. The manner by which gastrin leads to augmented gastric acid secretion is unclear. Kahlson et al[11] hypothesized that gastrin acts by facilitating release of histamine locally in gastric mucosa. Depletion of histamine stores in turn leads to the activation of the histamine-forming enzyme, histidine decarboxylase. Other investigators, however, speculate that gastrin may act directly to stimulate histidine decarboxylase activity leading to increased histamine production, which in turn stimulates the parietal cells.[12] In fact, pentagastrin enhances this enzyme activity 8-fold above control levels. Since secretin and an antigastrin compound, SC-15396, inhibit gastrin-stimulated gastric secretion, but do not depress histidine decarboxylase activity, their antisecretory potential would appear to be beyond histamine formation. However histamine-stimulated gastric secretion is not blocked by secretin. Hence, because of these confusing observations, the role of gastrin in the stimulation of acid secretion is still obscure. Nor does gastrin appear to act by stimulation of gastric mucosal adenyl cyclase activity with the resulting 3′,5′ cyclic AMP causing the acid secretion.[13] Further efforts are needed in this area.

Protein Synthesis. Johnson et al[14] have shown that pentagastrin stimulates the in vitro and in vivo incorporation of ^{14}C-leucine into protein of the digestive tract. How this trophic effect of the hormone is translated into augmented secretion is unclear. Additionally whether gastrin is important for rapid cell turnover and renewal of the gastrointestinal mucosal epithelial cells because of its effect on protein synthesis is also unclear.

Metabolic Fate. Very little is known about the metabolic fate and inactivation of gastrin. The N-terminal pyroglutamyl group endows the molecule with resistance to aminopeptidases, and the C-terminal amide group is resistant to carboxy peptidases. The C-terminal tetrapeptide amide (Try-Met-Asp-Phe-NH_2) can, as already mentioned, produce all the physiological effects of the entire molecule. The amide group on the C-terminal phenylalanine is essential for gastric stimulation and other hormonal actions. An amidase activity, catalyzing the hydrolysis of the amide group on the C-terminal phenylalanine, could provide a means of inactivation of the hormone. Laster and Walsh[15] studied several rat tissues for amidase activity and demonstrated hepatic and renal inactivation of gastrin following cleavage of the Phe-NH_2 linkage. Other investigators have shown biological inactivation of the gastrin molecule after intraportal injection, although immunoreactivity may be unchanged.

Clinically, measurement of circulating plasma gastrin concentrations is helpful. Several entities characterized by hypergastrinemia have been defined.

Zollinger-Ellison Syndrome. This syndrome first described by Zollinger and Ellison in 1955 is due to autonomous gastrin secretion by ulcerogenic, non-beta islet cell tumors of the pancreas. Astronomical serum gastrin concentrations are the rule (Table 1) as are gastrin concentrations in extracts of tumor tissue or its metastases.

Another cause of hypergastrinemia results from previous gastric surgery at which time a portion (usually small) of gastric antrum remains adherent to the duodenal stump and out of continuity with the acid secretory portion of the stomach. Hence there is a failure of gastric acid to inhibit gastrin release by this isolated tissue. An ulcer diathesis ensues until the remaining antral tissue is resected.

Some of the highest plasma gastrin concentrations have been noted in patients with pernicious anemia. Because of achlorhydria, stimulation of gastrin secretion is not turned off and continues unabated. However plasma gastrin levels fall promptly to normal after introduction of 0.1 N HCl into the stomach. Why gastrin secreting cells are spared in atrophic gastritis is an enigma.

Duodenal Ulcer. Plasma gastrin concentrations of patients with duodenal ulcer usually fall in the normal range. Since gastrin behaves similar to other hormones by responding to changes in concentration of a target substance, in this case hydrogen ion, any gastrin detectable in plasma seems paradoxical in view of the tendency of duodenal ulcer subjects to secrete more acid. Furthermore though fasting serum gastrin levels are not elevated in duodenal ulcer patients, the rise in serum gastrin in response to a protein-rich meal is exaggerated in these patients (a 71% increase when compared to an increase of 38% in normals).[16]

Table 1. Fasting Serum Gastrin Concentrations in Various Physiologic and Pathologic States

Source	Serum Gastrin, pg/ml
Normals	165 ± 28*
Peptic ulcer (all)	98 ± 12
Gastric ulcer	126 ± 41
Pyloro-antral ulcer	118 ± 6.8
Duodenal	82 ± 12
Z-E syndrome	1000 ± 300
Post V & A†	26 ± 4.9
Post V & P‡	123 ± 21

* Mean 1 S.E.
† Vagotomy and antrectomy.
‡ Vagotomy and pyloroplasty

Other investigators find fasting serum gastrin concentrations significantly higher in duodenal ulcer patients when compared to normal subjects and those with gastric ulcers. Following complete vagotomy for duodenal ulcer, serum gastrin levels fall to values even lower than normal, but after a protein meal serum gastrin increases significantly more than in patients with gastric ulcer subjected to similar surgery.

Serum calcium concentrations also influence gastric acid secretion and serum gastric concentrations. Both normal subjects and patients with a duodenal ulcer increase acid output and serum gastrin in response to hypercalcemia. Magnesium abolishes the effect of hypercalcemia on these parameters. Calcium appears necessary for both the initiation of basal acid secretion and its augmentation by a variety of stimuli. Serum calcium concentrations below 7.0 mg/100 ml are associated with marked decreases in acid output.[17] When gastrin is administered concomitantly with calcium, a synergistic affect on acid secretion is apparent. In the Z-E syndrome, calcium infusion augments plasma gastrin concentrations even after total gastrectomy, suggesting enhanced release of the hormone by this cation. Clinically calcium infusion with measurement of serum gastrin concentrations may help to detect the occasional patient with the Z-E syndrome whose fasting gastrin levels are borderline abnormal.

Although much is known about gastrin, much remains to be learned about its precise role in acid secretion, its metabolic fate, its role in "garden-variety" peptic ulcer disease, as well as further biological effects both on the digestive system as well as other systems. The advent of a radioimmunoassay has been instrumental in expanding our knowledge, and synthesis of a selectively labeled gastrin molecule should help answer some of these questions.

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Evidence of Chronopathology in Alcoholism*

RAY B. SMITH, PH.D., GLENN ROWINSKI AND KATHLEEN KRETZMER GERSTEIN

After withdrawing from alcohol many alcoholics admit going through periods of intensified craving or want for alcohol, interspersed with periods of relative disinterest in drinking. Our therapists, most of whom hold psychogenic theories of addiction, think that these periods of enhanced craving are generated by psychological stressors at such times.

In pilot interviews with 100 alcoholics it was found that drinking incidents were often associated with periods of "dry withdrawal," to use their phrase. That is, as in heroin addiction, our patients verbalized periods after withdrawal from alcohol in which they experienced many of the physical symptoms of withdrawal without having used alcohol again. A tentative hypothesis of some physiological cycle of demand for alcohol, a chronopathology, replaced strict psychogenic hypotheses in our laboratories.

One of the latest and most complete reviews of studies in chronobiology cites biorhythms with frequencies ranging from seconds, to months and even a year or longer.[1] The same review cites other studies that indicate alcohol can alter normal physiological rhythms, i.e., create new rhythms from genetically determined biorhythms.

Biorhythms altered in the course of alcohol addiction would fall under the heading of chronopathology: "Alteration in biologic temporal characteristics as a function of disease and as determinants of disease."[1] If there is a chronopathology manifested by recurring withdrawal symptoms—the well-known cure of such symptoms being the ingestion of alcohol, it would be useful to find the cycle and forewarn the alcoholic. Theoretically he would then be forearmed. In addition, the findings of such a cycle would be an important research breakthrough, indicating new methods of getting at the biochemistry of addiction and its interdiction.

The question asked in the present research is: Is there a physiological cycle of demand (for alcohol) in the abstinent alcoholic? One way of discovering such a cycle would be to follow 'withdrawn' alcoholics and make various physiological measurements and ask relevant questions. Another more possible way is to infer that if a man is trying to remain abstinent and doesn't, his lapse into drinking will most likely occur at or near the peak of any 'cycle of demand' present. By measuring actual lengths of sobriety, any motivating cycle should show up, extenuating circumstances such as major holidays, etc., being canceled out in the sampling procedure as far as possible.

Procedure

Four-hundred-thirty alcoholics were interviewed at various times over two years. Fifty-seven were interviewed at the beginning of the summer of 1969 (June), 121 in the winter of 1970 (December-January), and 252 at the end of the summer of 1971 (July-August). All were newly admitted to the District of Columbia's Rehabilitation Center for Alcoholics, Detoxification Unit, and although all were sober at the time of questioning, they had recently shown the usual physiological signs of withdrawal and were thereby labeled alcoholic.

In the interview they were asked two questions: (1) Were you trying to remain abstinent before your last drinking episode? and (2) How long did you remain abstinent just before the onset of this last drinking episode? The results were tabulated for those who indicated they were trying to remain abstinent (416 men), and their responses were categorized into weeks, months, and years of abstinence.

Results

Figure 1 shows the curves of the three different samples. There was no circadian-type curve as such, possibly due to the large percentage of the sample falling out of the distribution so early in the graph. The curve obtained, however, is different from that expected by either behavior or stress theories of drinking. A pattern of peaks developed, but unevenly after five months in each sample, suggesting that some factor or factors were operating differentially in all samples. It should be noted, however, that due to the marked differences in sample sizes and the small number of men still in the samples after month nine, one

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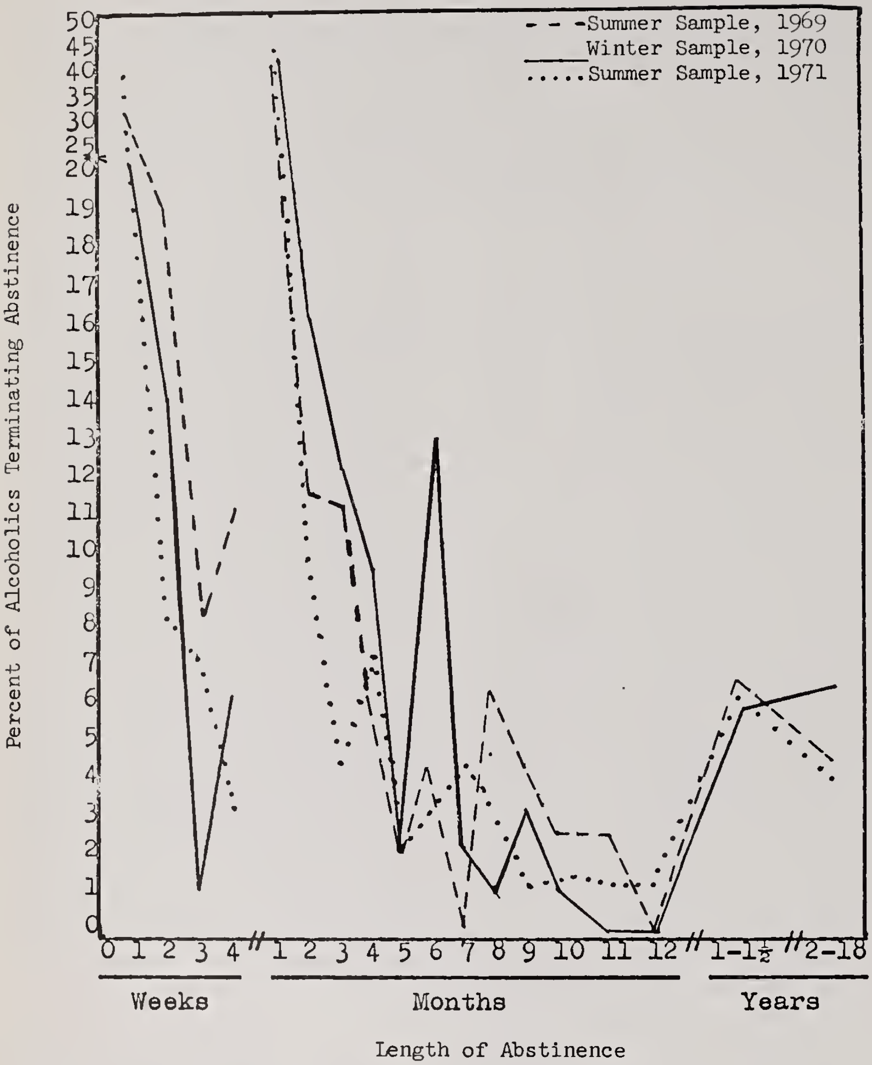

Fig. 1. Experience of alcoholics trying to maintain abstinence.

man in the summer of the 1969 sample losing abstinence carries the weight of five men in the summer of the 1971 sample in terms of height of the peak. A more representative curve is obtained in the graph in figure 2 in which all samples are combined. In this graph it can be seen that for months one through three the curve is similar to that which would be expected from behavior theory, in which the distance in time from the re-inforcer is linearly related to the strength of the drive. After month three, and certainly after month five, the linear relationship no longer holds, or doesn't appear to. A problem still obtains in figure 2 as in figure 1. The large number of men leaving the sample early do not give a picture of what their subsequent behavior would have been had they continued their abstinence longer. To cancel out much of this effect, figure 3 was plotted, showing the per cent of men terminating abstinence during a given period, but, basing the percentage figure only on the total number of men remaining abstinent at the beginning of the period, the per cent was calculated. This graph indicates that the urge to drink appeared to have similar strength at months two, four and six, and during the first week of abstinence. Conversely, it was similarly lacking or at least reduced in intensity in the third and fourth week of abstinence and in months five, eight, and 12.

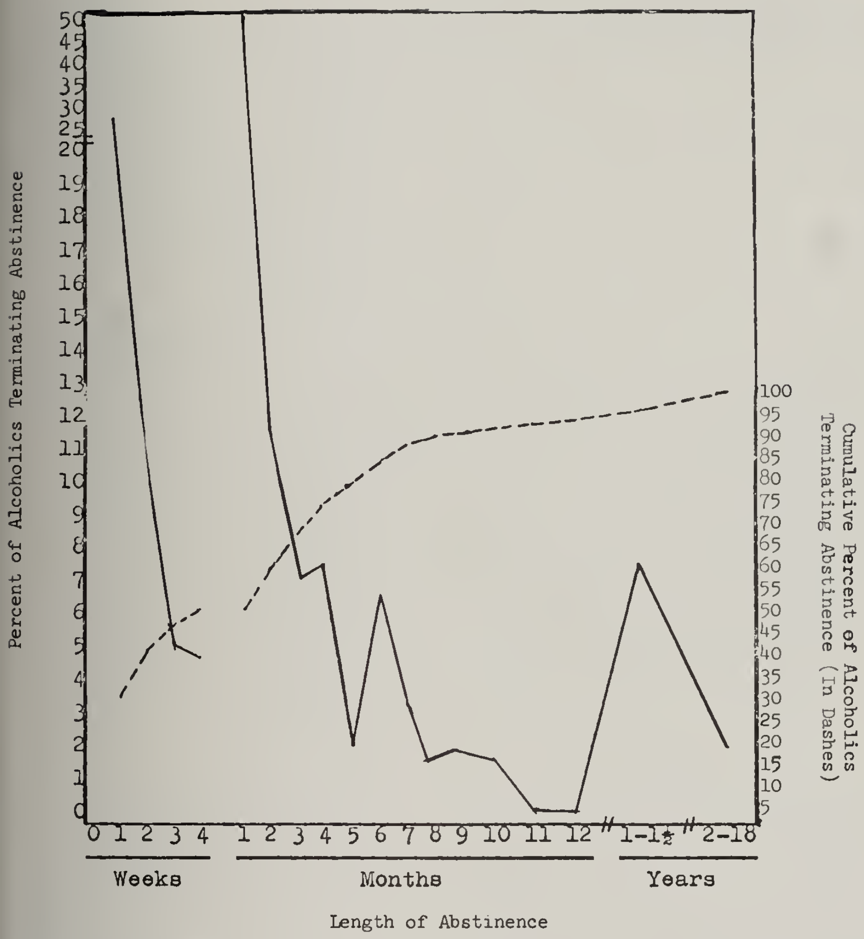

Fig. 2. Experience of alcoholics trying to maintain abstinence combining all three samples. N = 416.

Further, the distance between the peaks widened with time. This outcome would be expected if a normal biocycle were interrupted and/or restructured by alcohol, and over a period of abstinence the chronopathology gradually gave way to the original chronobiological rhythm.

In figure 2 a cumulative curve is plotted against the right ordinate. Such a curve might be of interest to an alcoholic attempting to maintain abstinence. For example, if he is sober at the end of a month, he can know that he has held out longer than 50% of the men who "fell off the wagon" within a year and a half in our sample. Similarly, by the end of four months of abstinence he has achieved longer sobriety than 75% of our sample. Fewer than one in 10 men sampled made it through a year of sobriety. On the other hand, almost 8% of the sample began drinking again after over a year but fewer than 18 months of sobriety, indicating that the curve does not flatten after 12 months and that danger still exists.

Discussion

There appears to be a definite chronopathology in alcohol addiction, as represented by our sample of 416 alcoholics who were trying to maintain abstinence and did not. The curve as plotted in figure 3 indicates that the cycle may be alcohol-specific in terms of a gradual reduction in amplitude and distance between the peaks. On the other hand, alcohol is known to interfere with many areas of normal

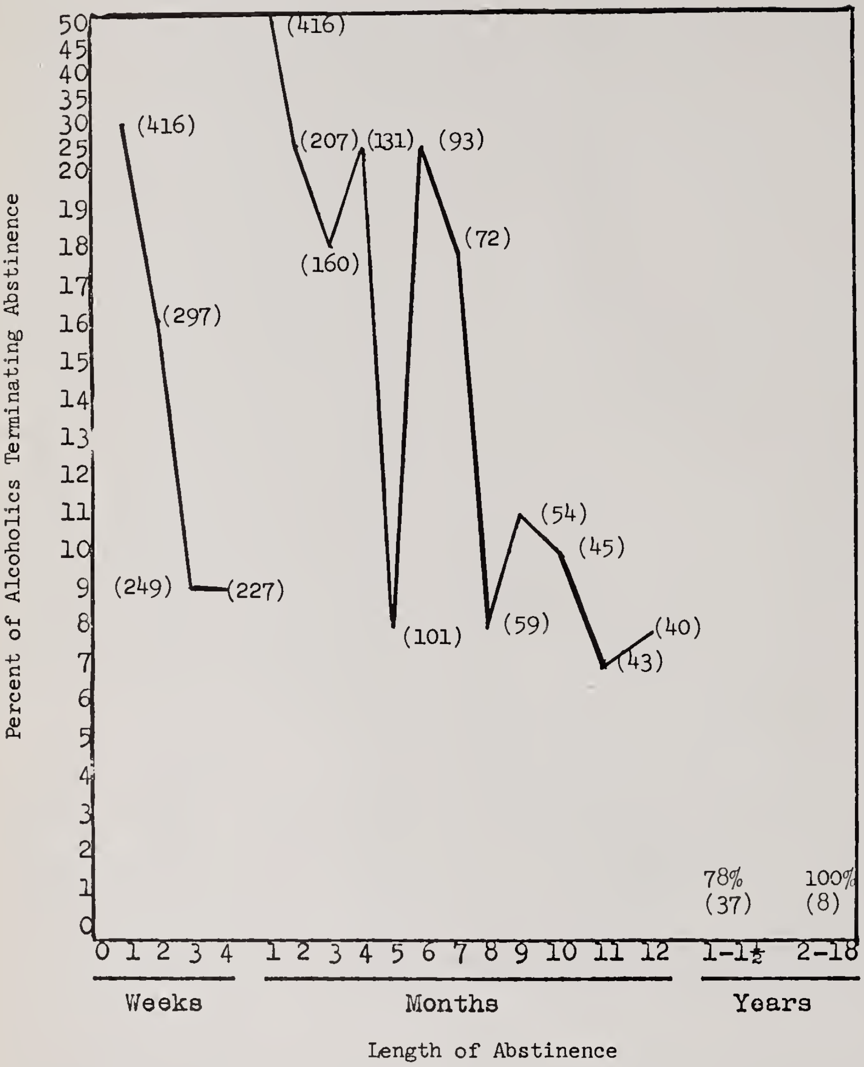

Fig. 3. Men terminating abstinence, plotted by number of men (given in parenthesis) still abstaining at beginning of each period plotted.

body functioning, many of which may have their own biorhythm. If alcohol's chronopathology is tied in with one of these, the graph in figure 3 may represent a gradual reduction in the effect of alcohol in altering the normal cycle of one or another previously existing biorhythms.

Another question that could be asked is whether the chronopathology attributable to alcohol addiction ever finally loses its effect or subsides. Immediately following the question would be the question as to how easy is it to instigate a new cycle of chronopathology in the alcoholic once a period of abstinence is terminated by renewed drinking.

The curve obtained is not explainable by behaviorism theories, since it is not linear or asymptotic. It certainly does not lend itself to psychogenic theories of psychologically induced or stress motivated drinking in alcoholics, since in that case the renewed drinking pattern would randomize into a flat curve. Stress, if it is a factor in generating the findings of this study, is internal or biochemical in nature. As such, the biochemical changes can be found through further research, the significant ones noted, and the physiological demand for alcohol altered or even halted medically.

Meanwhile, many of our patients have reported that a foreknowledge of a rhythmic urge to drink has been of value in helping them maintain abstinence for increased periods of time. This information may have immediate and direct use for the practicing physician.

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Detection of Aspirin Sensitivity by Pulmonary Function Tests

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The unpredictability of aspirin-induced asthma, both temporally and in intensity has been of major concern to physicians for many years. Such attacks have not infrequently been associated with the need for intensive treatment, which is not always effective in saving the patient's life.[1-5] Most physicians, being aware of the potential danger, withhold aspirin from any patient with nasal polyps and asthma. In view of the potential by serious reactions which might occur, one can hardly argue against this rationale, although it is obvious that not all patients with nasal polyps and asthma develop aspirin sensitivity. In addition, the use of aspirin may be very important in the treatment of hyperpyrexia or as an analgesic in such conditions as rheumatoid arthritis. Unfortunately, the use of other analgesics, such as indomethaein (Indocin) or dextropropoxyphen (Darvon) does not necessarily solve this problem.[6,7] Tests for an immunologic mechanism have been inconclusive,[1] so that at the present time there remain no guidelines to follow in determining which patients with nasal polyps and asthma can tolerate aspirin. This is extremely important, since it is well documented that patients can ingest aspirin for years without change in their clinical status.[5] By measuring pulmonary function in a double-blind placebo study, I hope to show that the patient who ultimately develops intractable asthma after ingestion of aspirin would at an earlier time have had subclinical changes, as illustrated by a statistically significant fall in FEV_1, TVC, and MMEF.

Methods

Five patients with proven idiopathic asthma (on the basis of physical examination and history of negative or insignificant skin tests), nasal polyposis, and no history of aspirin sensitivity were studied. Evaluation was dependent upon clinical stability, that is, the patient should not be using more of his medication than usual to control his symptoms. Corticosteroids were reduced to a minimum dosage that prevented asthma. If the patient was taking alternate-day steroids, testing was done on the off day. Testing was not carried out during an acute flare-up of asthma in order to insure safety for the patient and a stable baseline.

These patients were evaluated by history, physical examination and pulmonary function-FEV_1, TVC, and MMEF (forced expiratory volume in one second, total vital capacity, and mid-maximal expiratory flow) before during and after the ingestion of five grains of aspirin and a placebo (table 1). Before the ingestion of either placebo or aspirin a history was taken and a physical examination done, including vital signs. Baseline pulmonary function tests were then done. Following the ingestion of capsule A (its exact nature being unknown to the physicians involved with the testing), the patient was evaluated for subjective symptoms, auscultatory findings, conjunctivitis, rhinorrhea, and change in pulmonary function every hour for three hours. Blood salicylate levels were drawn at two hours after the ingestion of capsule A. The patient was then given capsule B (same size, shape and color) and was evaluated at hourly intervals for three hours. Again blood salicylate levels were determined two hours after the ingestion of capsule B.

Results

As noted in table 2, there was a slight increase in objective findings on auscultation of the lungs in patients one, two, and four. In all three patients there was an increase from wheezing on forced expiration to diffuse wheezing of a minimal nature (with excellent air-exchange) but without associated subjective change of significance. In none of the patients was there associated conjunctivitis, rhinorrhea, cutaneous flushing, or dyspnea. There was no essential change in pulmonary function values, either after aspirin or placebo except in patient four, who showed a significant fall in parameters after receiving

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TABLE 1. Pulmonary Function Following Aspirin Ingestion in Five Patients (Liters per minute)

	Patient				
	1	2	3	4	5
MMEF					
Baseline	85	45	48	118	90
1 hr. post ASA	73	60	45	71	86
2 hr. post ASA	86	68	50	63	86
3 hr. post ASA	90	68	39	58	80
1 hr. post placebo	93	60	46	56	82
2 hr. post placebo	82	57	42	55	86
3 hr. post placebo	84	63	39	40	90
	1	2	3	4	5
VC					
Baseline	2050	1625	1700	2533	2100
1 hr. post ASA	2050	2183	1750	2131	2050
2 hr. post ASA	2083	2117	2000	2167	2050
3 hr. post ASA	2150	2143	1850	1967	2100
1 hr. post placebo	2150	2033	1740	1883	2150
2 hr. post placebo	2166	2200	1750	1917	2200
3 hr. post placebo	2133	2116	1700	1791	2150
	1	2	3	4	5
FEV					
Baseline	1110	750	1200	1650	1100
1 hr. post ASA	1466	1083	1200	1200	1250
2 hr. post ASA	1500	1250	1400	1200	1200
3 hr. post ASA	1650	1183	1200	1025	1250
1 hr. post placebo	1650	1050	1150	983	1400
2 hr. post placebo	1566	1016	1150	958	1450
3 hr. post placebo	1600	983	1150	791	1500

TABLE 2. Clinical Status and Salicylate Levels at Time of Pulmonary Function Tests (mg. %)

	Patient				
	1	2	3	4	5
Objective change (lungs)	Slight	Slight	0	Slight	0
Subjective change	0	0	0	Slight	0
Salicylate levels					
2 hr. post ASA	2.0	1.8	2.2	2.6	2.2
2 hr. post placebo	1.6	1.1	1.7	1.6	1.8

aspirin first. This patient had a 28% fall in TVC, a 52% fall in FEV, and a 67% fall in MMEF. A fall of >15% in any of these pulmonary functions was considered significant. For this reason alone it is necessary to know the patient's history in more detail. Of interest also is the fact that previous studies have shown salicylates in the blood for less than 30 minutes after ASA ingestion.[8]

The patient, R. N., is a 41-year-old white male department store manager with a history of wheezing since the age of 12. There has been no known relationship to seasonal or environmental allergens, and the patient is now requiring daily steroids for control of his asthma. In June 1969 he had a bilateral nasal polypectomy performed at the University of Michigan Medical Center. Skin-testing, except for grass pollen which had no correlation with his symptoms, was negative, nor did any of his skin tests explain his perennial symptoms of asthma. His father had a similar history of asthma, aspirin-sensitivity, and nasal polyps and died during an acute asthmatic attack.

Discussion

Probably one of the most interesting and clinically important entities in medicine is the dramatic association of asthma, nasal polyps, and aspirin-sensitivity. It is, therefore, somewhat strange that there is not uniform agreement in the literature that asthma and nasal polyps may predispose a patient to aspirin-sensitivity. In addition, while it is well recognized that patients with asthma may also have nasal polyps or aspirin sensitivity, there is debate on the frequency with which this occurs.[9-12] There is also disagreement on the type of asthma involved. Despite early studies, there does not appear to be any association of nasal polyps with infectious asthma.[13] Some studies have emphasized that nasal polyps and ASA sensitivity are correlated with allergic asthma and other atopic conditions.[14-16] However, as early as 1928 Van Leewen[17] demonstrated the absence of a personal and family history of atopy in parents with this triad as well as failure to show wheal and flare

medical annals of the district of columbia

vol. 42 no. 2 february 1973

reactions with pollens and other inhalants. Samter and Beer[5] more recently have presented impressive evidence for a triad of nasal polyps, aspirin-sensitivity, and idiopathic asthma. My experience has been similar to theirs.

Characteristically, the patient who ultimately develops aspirin-sensitivity develops intermittent symptoms of "vasomotor" rhinitis with profuse watery nasal secretion, chronic nasal obstruction, and finally nasal polyps. The first episode of asthma, beginning in middle age, is rarely related to a well-defined precipitating factor. It is distinguished initially by its impressive reversibility with bronchodilators and better response to smaller doses of steroids than immunologically induced asthma. The nasal and bronchial symptoms may precede the development of ASA intolerance by months or years. Not only is there a lack of correlation between the frequency of ASA ingestion and the severity of asthma when it develops, but the initial reaction is often unexpected and not attributed to the drug.

Although salicylates other than acetylsalicylic acid fail to produce symptoms, exposure to certain strong or minor analgesics such as indomethacin (Indocin), dextropropoxyphene (Darvon), and mefamic acid (Ponstel) may not only produce symptoms but may be associated with a significant decrease in pulmonary function studies.[7] Also, exposure to certain chemicals structurally related to aspirin can induce "aspirin-like" symptoms, as typically occurs with hydrazine yellow (Tartrazine) used in food coloring (soft drinks, canned vegetables, and other foods) and even as coloring for medication such as Quibron, ironically a bronchodilator used in the treatment of asthma.[18,19]

Symptoms in aspirin-induced asthma may occur immediately but usually within 20 minutes and up to two hours after ingestion of ASA. Profuse watery rhinorrhea initially is often followed by scarlet flushing of the head, neck, chest and extremities, nausea, vomiting, abdominal cramps and diarrhea, and, finally, wheezing without cough or cyanosis. Epinephrine and aminophylline will usually control reactions within 2 hours, but malaise and increased bronchial secretion can persist for several days.

There has been much written about possible immunologic mechanisms involved in aspirin-sensitivity, but at the present time tests for the mechanics involved have been inconclusive. Skin tests to ASA are usually negative and dangerous.[20] Lymphocyte transformation, indirect hemaglutination, immunogluoresence, PCA, microprecipitation tests, and utilization of the rat mast-cell technique in ASA-sensitive patients have shown no evidence for an immunologic reaction. Serum IgE levels are at the lower limits of normal,[20,21] and passive transfer to subhuman primates has failed.[22] For this reason, interest has centered on other means of evaluating these patients. McDonald, Stevenson and others[23] have recently challenged 42 patients with nasal polyps and asthma with 640 mg ASA. Eight of these patients showed a reduction of greater than 50% in FEV_1. However, unlike my patient, they all had ocular injection, profuse rhinorrhea, cutaneous flushing, and severe dyspnea. This may be a reflection of the smaller dose of ASA 1 used for challenge, but I feel that the ability to detect those patients with latent aspirin sensitivity even before the onset of symptoms is an essential part of such studies. Certainly these studies need to be continued with larger groups of patients, with the hope that they will allow the physician to predict which patients are likely to develop life-threatening asthma after ingestion of acetyl salicylic acid.

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Psychiatric Aspects of Addison's Disease: Report of a Case

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The physician is confronted on a daily basis by numerous examples of body language that the patient cannot put into exact and helpful words and that cannot be documented by laboratory findings. With time these cases usually reveal their more specific nature either in terms of a clinically definable psychiatric disorder or an illness amenable to treatment offered by the other branches of medicine, not infrequently both. The following case presentation is an illustration of the latter situation. Addison's disease, since its original description in 1855, has been recognized as containing integral psychiatric aspects, but an opportunity to follow such a situation in combined medical treatment rarely occurs.

Report of Case

The patient, a young, unhappily married white woman, first came for psychiatric consultation in August of 1971. At that time she appeared to be a distraught and anxious individual. An intermittent pallor was present and at times her skin appeared to have a slight yellowish tinge. The facial expressions varied between lethargy and moderate discomfort. Attention span was shortened, but she was lucid and well oriented. The thought processes were then focused upon her poor marital situation, infatuation with her employer, and her poor physical condition. The mood was depressed. There was repeated mention of nausea and vomiting, the latter of more recent origin (two weeks), the former accompanied by gagging, usually present when the patient encountered stressful situations. Vague suicidal thoughts and fears were present. Memory was intact and intelligence above average. The patient had little insight into her difficulties. She stated she came to my office following two weeks of being acutely anxious, depressed and physically uncomfortable. During the beginning of that period she had confessed to her supervisor that she had had long-standing affectionate feelings toward him and shortly thereafter began developing intermittent nausea and vomiting. A week before I first saw her she had a gastrointestinal x-ray examination and gastroscopy, which were negative. She denied any similar emotional or physical episodes in the past, but later a history of provocative and impulsive behavior came to light along with many unrealistic and maladaptive patterns. The family constellation is comprised of the following: two older siblings, both relatively successful, unmarried and living at home; a father who has had diabetes for six years and is on moderate doses of insulin, and the patient's mother, who is in good health. The paternal grandmother had been afflicted with presenile dementia for a long time before her death.

The initial impression was that of a patient suffering from a hysterical personality disorder, possibly of the more primitive type, along with a strong depressive component and a predisposition to somatize her conflicts, but a physical complication had not been ruled out. Follow-up consultation and psychiatric treatment were recommended. The patient was initially seen on a twice weekly basis for two weeks, during which time the anxiety, depression and agitation increased along with the nausea and emesis. She began to form an abnormally dependent relationship with her psychiatrist, became increasingly withdrawn, and at times exhibited inappropriate behavior bordering on the bizarre. Due to these factors and the increasing physical debilitation, psychiatric hospitalization for observation was considered. Thorazine in the amount of 25 mg was given twice daily in an attempt to control the vomiting and assay any effect it might have on her emotional disturbance. This was ineffective, and she was hospitalized in a psychiatric facility. At this time she began to have dizziness and weakness. An initial hospital blood pressure reading showed the patient to be hypotensive, but this was variable in nature, the pressure fluctuating between 100/60 and 60/40 sitting. The Thorazine was discontinued at this time. Physical examination performed by an internist showed questionable 'butterfly' pigmentation over the nasal area and hyperpigmentation of the areola. This, along with the pernicious vomiting, hypotension and psychiatric aspects raised the possibility of Addison's disease. The patient was transferred to a medical ward of a University Hospital with psychiatric follow-up, where diagnostic studies and the clinical course confirmed the presence of this entity.*

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Following this diagnosis, treatment with cortisone acetate and other supportive measures were initiated, and the patient showed a significant decrease in her depressive state along with a remission of the nausea, vomiting, and anxiety. The serum sodium level began to return to normal, and there was a lessening of the emotional withdrawal along with an almost complete resolution of some of the more bizarre features of the disorder. The excessive dependency and provocative behavior remained.

The patient was discharged with continued medical follow-up and a course of psychotherapy advised, directed at helping her work through the more prevalent inter- and intrapersonal conflicts, deal with the underlying depression, and to function more adequately within the bounds of her personality and physical disability.

The patient has been followed 12 months now, and there have been two recurrent episodes of emesis and one severe depressive period during the first two weeks of January 1972, during which time a serum sodium level of 131 mEq/L was noted. She has continued to act-out her underlying conflicts and use her physical illness to her disadvantage at times, but these tendencies have been ameliorated. Perhaps the most striking psychiatric aspect of the treatment has been a marked reduction in the provocative fantasies and acting-out directed toward others, along with a concomitant return of pleasure in her personal and work relationships. These latter events have occurred during the past four months.

Discussion

A review of the neuropsychiatric-like symptoms of Addison's disease and the differential diagnosis was made by Drake in 1957.[1] This patient exhibited many of the more generalized accompaniments of the illness, such as easy fatigability, progressive weakness, anorexia, weight-loss, and at times threatened collapse and syncope, which can all too easily be ignored or misinterpreted until one is faced with a true Addisonian crisis such as she appeared to be entering at the time she was transferred to a medical ward. The most outstanding features of this patient were nausea and vomiting, which first led to thoughts of a gastrointestinal disorder and depression along with a histrionic component that suggested a more clearly defined psychiatric disability. During the prodromal phase the patient presented a diagnostic challenge of differentiating organic from functional. The gastrointestinal signs and symptoms so impressed the physician first consulted that a full-scale search into this area was launched to no avail. Shortly thereafter the patient came into psychiatric treatment for her increasing feelings of anxiety, depression, and physical discomfort. Finally, with hospitalization for further evaluation, the fact that the patient had a combination of medical difficulties, namely Addison's disease, a depressive neurosis, and a hysterical personality construct varying from the normal became clear.

A few points may profitably be mentioned at this juncture regarding the danger of missing the diagnosis in such cases. At the time of initial hospitalization the patient was in the early stages of an Addisonian crisis with a possible fatal outcome if undetected. The simple task of recording routine blood pressures at that time was invaluable in establishing early ongoing physiological changes and indicating a need for more intensive management, along with the discontinuation of Thorazine. The case of a patient with unknown Schmidt's syndrome being treated initially with Thorazine which possibly acted synergistically in an already hypotensive situation is discussed by Harper and Earnshaw.[2]

The fact that the patient has continued in psychiatric treatment long after the acute symptoms were brought under control is remarkable and has supplied documentation of an underlying depressive neurosis in a basically hysterical personality. A fixation on the easily controlled physical symptoms has been prevented, and the patient finds it difficult to use these as a defense against making progress in her psychiatric treatment. A description of some of the psychodynamic aspects of Addison's disease has been offered by Wallerstein et al[3] in which they mention the meshing of some of the signs and symptoms such as weakness, tiredness, and withdrawal from active social roles with the underlying reactive patterns a particular patient has evolved to meet a lifetime of changing stresses. This case, which has provided significant anamnestic data over a considerable period of time, tends to correlate with this observation.

Bunney et al[4] remarked in their study of hospitalized depressed patients that the patients showing wide fluctuations in the excretion of urinary steroids showed the widest variation in behavioral ratings of depression and anxiety. Although no data was available until a few days following the patient's hospitalization, perhaps the growing erratic performance of the adrenal cortex was responsible for much of the earlier observed disruptive behavior. It is tempting to try and correlate the patient's depressive tone with a lowering of her cortisol output, but studies done by Bunney, McClure, Grinker and others tend to refute this, since they constantly found higher plasma 17 hydroxycorticosteroid levels in depressed and anxious patients. McClure stated that his values were highest between 6 and 8 A.M. and offered this as a possible explanation for the classical increase in depressive feelings in quite disturbed patients during the early morning hours. He also noted a correlation in four depressed patients treated with amitriptyline (Elavil) and imiprimine (Tofranil) between a fall in plasma cortisol level and a decrease in depressive feelings. The case reported by N. D. Rizzo et al[8] in their studies of a cyclothymic patient, who on closer reading appeared to have been schizophrenic and in whom psychological overactivity, urinary glucocorticoids were very low and increased with recovery is somewhat puzzling. There was no clear-cut variation in the excretion of urinary 17-ketosteroids. Bliss et al[9] claimed that the adrenocortical and pituitary adrenocortical reactivity of schizophrenics and a control group were equivalent.

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* Diagnostic laboratory data and a chart of the hospital course available upon request.

This patient's low serum sodium level served as a convenient, although indirect guide to her adrenal cortical functioning and mental status. Though low (113 mEq/L upon admission), she never experienced a true organic brain syndrome, but the low sodium levels seemed to occur simultaneously with increased depressive feelings, anxiety, and gastrointestinal distress. It is interesting that the one sodium level of 131 mEq/L obtained in January 1972 corelated with an exacerbation of the depression the patient was experiencing during her course of psychiatric treatment. At that time the only medication she was on was cortisol acetate. At present she is functioning at a higher level than when she was first seen. She is working regularly and enjoying a more normal marital relationship. Maintenance treatment consists of cortisol acetate and Florinef. She is not on any psychiatric medication, but is progressing satisfactorily as an outpatient.

Acknowledgement

The author wishes to express his appreciation to Drs. Michael M. Shefferman and John F. Mermel for their astute management of the endocrinological aspects of the case and their awareness of its psychiatric implications.

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Unusual Metastases from a Transitional-Cell Carcinoma of the Renal Pelvis and Ureter*

WILLARD A. BURNS, M.D.† AND ATTILA T. KADAR, M.D.‡

Transitional-cell carcinoma of the renal pelvis comprises less than 10% of renal tumors and has metastases in less than half the cases.[1,2] These tumors most frequently metastasize to lymph nodes; bones, liver, lung, and less frequently to the myocardium, thyroid, kidney, adrenal glands, and brain. We are reporting the first case of metastases from a transitional-cell carcinoma of the renal pelvis and ureter to a chromophobe adenoma.

Report of Case

A 78-year-old Negro was admitted to the Veterans Administration Hospital, Washington, D. C. on October 9, 1970 from a nursing home with chief complaints of temperature elevation, dehydration, vomiting, diarrhea, cough, rales, and vague pains for two days. The patient was unable to give a good history. In July of 1966 he had a left nephrectomy and partial bladder resection for a transitional-cell carcinoma of the renal pelvis and ureter. He had residua of an old cerebral vascular accident and arterio-sclerotic heart disease. The history and review of symptoms were otherwise noncontributory. The blood pressure was 140/100, the pulse rate 100, the temperature 101° F, and the respiratory rate 16. The patient was cachetic, dehydrated, and responded only to verbal stimuli by turning his head. The pupils were of pinpoint size. There were coarse rales and rhonchi in both lungs. The abdomen was distended, and ascites was present. The liver and spleen were not enlarged, but there was a left-sided abdominal mass. The urinary bladder was distended to the umbilicus. The extremities were very thin. No lymph nodes were palpable. Chest X-ray films revealed diffuse patchy infiltrates. Abdominal X-ray film was clear. An ECG revealed sinus tachycardia and low voltage. The impression on admission was cachexia, dehydration, and recurrent carcinoma. The hematocrit was 34%, and the white blood cell was normal. Glucose was 91 mg/100 ml, BUN 68 mg/100 ml, sodium 144 mEq/L, potassium 4.9 mEq/L, chlorides 107 mEq/L, CO_2 26 mEq/L, and calcium 7.7 mg/100 ml. The patient was given IV fluids and other supportive therapy but had a downhill course and was found dead in bed on November 17, 1970.

Postmortem Examination. The heart weighed 310 gm. The coronary arteries had a moderate degree of atherosclerosis. There was no evidence of old or recent infarction. The lungs weighed 550 and 380 gm. Gross evidence of tumor was not seen. The abdominal cavity showed a left subdiaphragmatic mass measuring 20 x 18 cm which was a cystic organized hematoma with tumor in the capsule. The liver weighed 1,250 gm, and the surface was finely granular. Cut surface showed a nodular pattern with multiple yellowish-red-brown areas of geographic infarction with tumor. The left kidney was surgically absent. The right kidney and bladder showed no evidence of tumor. The thyroid, adrenals, pancreas and testes were normal. The pituitary gland measured 3.5 x 3 cm. It was light brown, soft, and contained two whitish-yellow tumor nodules within the parenchyma measuring 0.6 x 0.6 and 0.9 x 0.9 cm respectively (fig. 1). Normal pituitary tissue was not identified grossly. The brain showed a striking distortion of the optic chiasma with marked thinning and loss of both

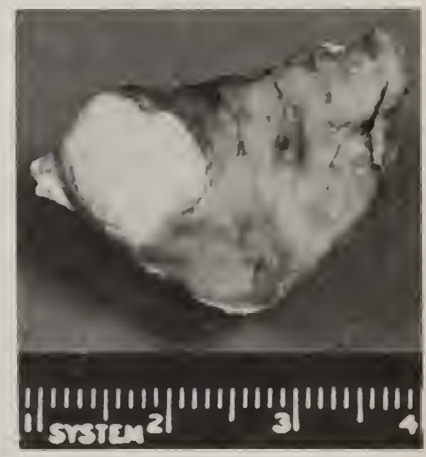

FIG. 1. Hemisection of adenoma with metastatic nodule (left).

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of the prechiasmal optic nerves, right more than left. The chiasma was similarly distorted.

The tumor seen in the liver and in the wall of the organizing hematoma was a well differentiated transitional-cell carcinoma similar to the specimen resected in 1966. Metastases were present in the lungs, periadrenal tissue, thyroid, periaortic lymph nodes, lumbar vertebrae, and paravertebral soft tissue. The nodules in the pituitary adenoma were also transitional-cell carcinoma (fig. 2). The adenoma was composed of uniform cells which by special stains (Orange G-PAS and Mallory's aniline blue) failed to demonstrate any granules. Compressed pituitary tissue was seen at the edge of some sections.

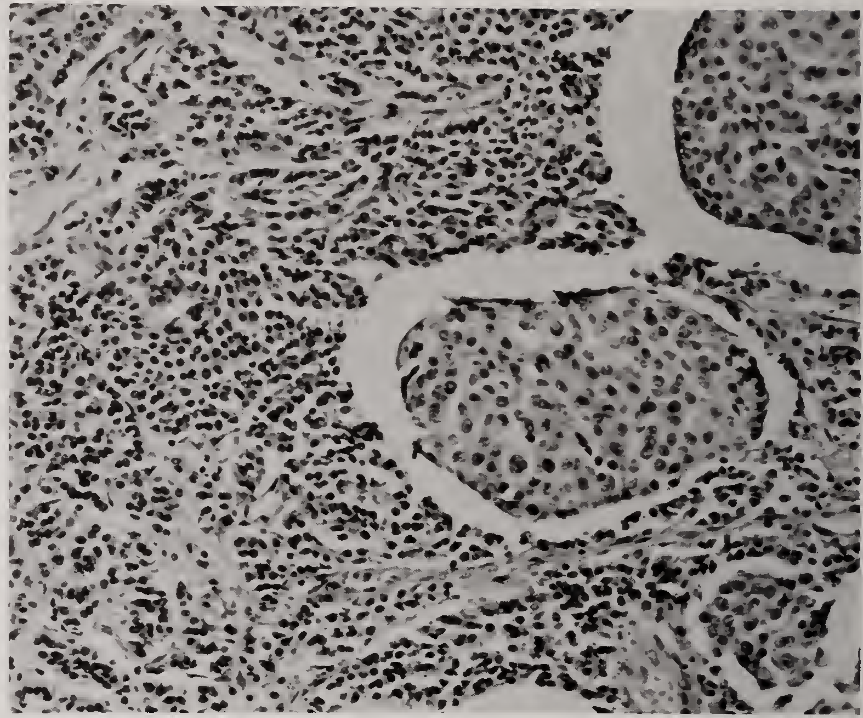

FIG. 2. Adenoma (left) with islets of metastatic carcinoma (right).

Comment

Recently the first case of metastases to a pituitary adenoma was reported in an excellent review article on neoplasm to neoplasm metastases.[3] The patient had undergone hypophysectomy for an adenoma. Metastasis was not seen, but one year later at autopsy metastases from a breast carcinoma were present in residual portions of the adenoma. The authors pointed out that when the host tumor is benign and the metastasis malignant the host tumor is usually endocrine, as in this case. The aspect of this case which is different is that the patient had no previous neurosurgery. The role of surgery in possibly altering cranial metastatic patterns has been pointed out by Smith et al[4] in their review of 35 metastasizing neuroectodermal tumors of the central nervous system. Extracranial metastases were present only in individuals who had previous surgery. They point out that without surgery cranial tumors very rarely metastasize outside the dura. The previously reported case had no evidence of metastases at surgery, and the metastases to the residual adenoma was found only at autopsy.

We were unable to find in the literature another case of a transitional-cell carcinoma metastasizing to a pituitary adenoma or how frequently tumors of the renal pelvis metastasize to the pituitary. It is undoubtedly less frequent than in carcinoma of the breast, which is cited as the tumor metastasizing most frequently to the pituitary. We think that our case of metastasis to an adenoma without previous neurosurgical intervention is best explained on the basis of coincidence in someone with an available "host" chromophobe adenoma.

We have reported the first case of a transitional-cell carcinoma of the renal pelvis and ureter with metastasis to a chromophobe adenoma of the pituitary gland. This was found at autopsy four years after nephrectomy, occurred without previous neurosurgery, and is probably best explained as a coincidence.

Acknowledgment

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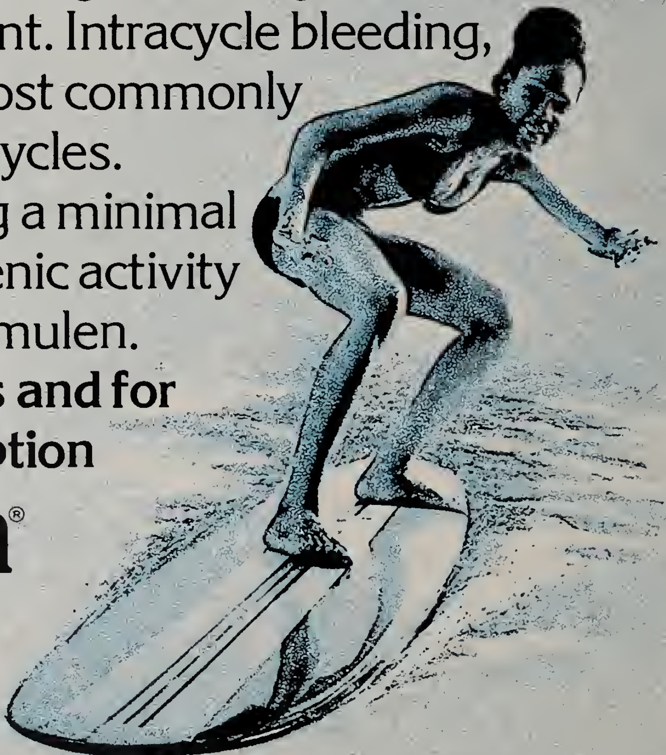

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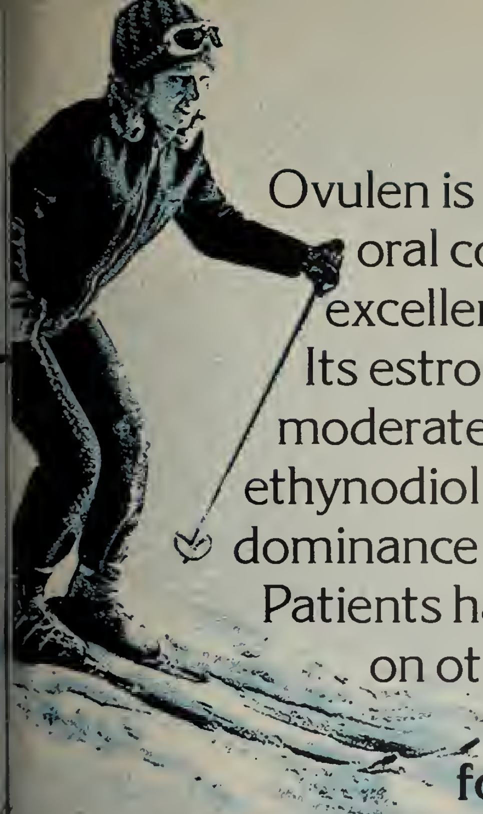

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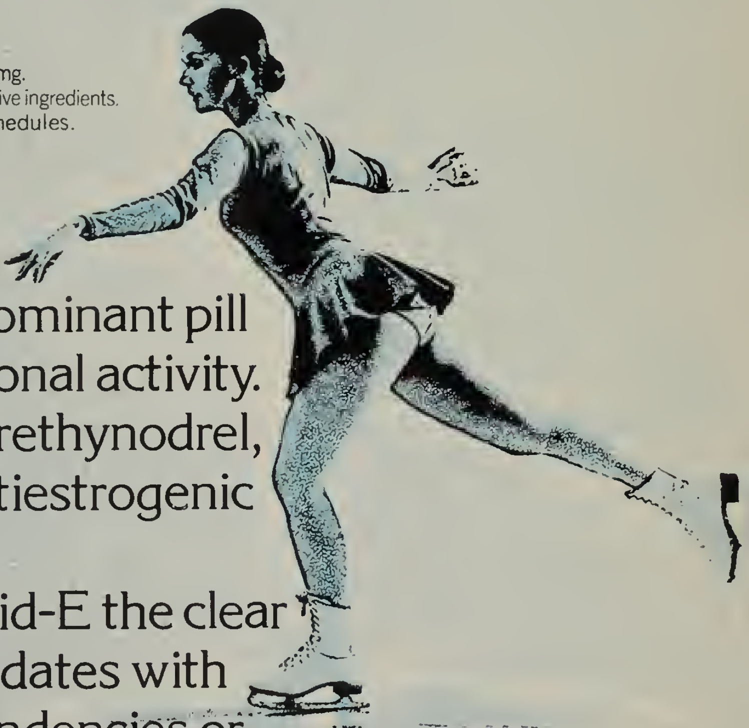

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Special note—Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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- Nayab Ali
- Michael Seremetis
- Melvin Small
- Charles Tartaglia
- Walter Y. K. Goo(R)
- Henry W. Williams, Jr.

Correctional Institutions

Francis L. Wenger, *Chairman*

Paul B. Cornely, *Vice-Chairman*

- Robert R. Belton
- Harry S. Bernton
- Peter R. Breggin
- Frank A. Caprio
- Dorothy B. Ferebee
- Frank A. Finnerty, Jr.
- Forest K. Harris II
- Robert E. Lee
- Leonardo C. Maquigad

Drug Dependency Committee

Frank A. Caprio, *Chairman*
Medical Society of D.C.

Allen Mondzac, *Vice-Chairman*
Medical Society of D.C.

- Mr. Rimsky Atkinson
  - Oak hill Children's Center, Laurel
- Maxwell Boverman,
  - Medical Society of D.C.
- Warren Brill
  - Medical Society of D.C.
- Ashur C. Chavoor,
  - D.C. Dental Society
- Ranville Clark
  - Medical Society of D.C.
- Victor Cohn
- Charles Colao
  - Medical Society of D.C.
- Miryam M. Davis
  - Medical Society of D.C.
- Brant W. Ditmore, D.O.
  - D.C. Osteopathic Society
- Sgt. Walter Milam
  - Metropolitan D.C. Police Dept.
- Robert DuPont
  - Medical Society of D.C.
- Michael Durr
  - Medical Society of D.C.
- Walter Faggett
  - Medical Society of D.C.
- Ricardo Galbis
  - Medical Society of D.C.
- Frederic Geissel
  - D.C. Pharmaceutical Association
- Howard Hoffman
  - Medical Society of D.C.
- Richard Kelly
  - Medical Society of D.C.
- Martin Levy
  - RMP
- Thayer MacKenzie
  - Wash. Psychiatric Society
- Don T. Mosher
  - Medical Society of D.C.
- Samuel Moskow, M.D.
  - D.C. Podiatry Association
- Raymond Osbourn
  - Medical Society of D.C.
- Pearl Holly
  - Medical Society of D.C.
- Michael Hart(S)
- William E. Sill, Jr.
  - Medical Society of D.C.
- Robert Stolar
  - D.C. Health Dept.
- Fred West
- Norman R. Tamarkin
  - VA Hospital, Drug Treatment Program

Emergency Drug Treatment

Margaret Abernathy, *Chairman*
Ann Lux (Psy), *Vice Chairman*

Sidney Berman
Mrs. Esther Greene
Donald Borcherding
Robert DuPont
Mr. Michael Greene
Stanley Samms
Charles Hayman
Thomas Piemme
John R. Tietgen

Emergency Medical Service

Harry Zehner, *Chairman*
William Matory, *Vice-Chairman*

Maurice Casey
James K. Cooper
George W. Hyatt
Hugo Keunen
Edwin C. Mitchell
Thomas Piemme
James P. Shaper
Steven Aurecchia(S)
Michael Green(S)
Warren J. Strudwick
Boris G. Vlaukin
Michael Green (Med. Student)
Joseph R. Young
Samuel Zola
J. D. Head
Raymon A. Noble
Robert Goodwin(S)
Roger Shelling(S)

Environmental Health

George Green, *Chairman*
Halla Brown, *Vice-Chairman*

W. Montague Cobb
Stuart Danovitch
Richard Feinberg
Harvey Gold
P. A. Gorman
Paul Jacquet
Michael Lemp
Thomas McMahon
Herbert Moskovitz
Morton H. Rose
Henry Palacios
Philip Pease
Robert Havell
Melchoir Savarese
James Schoettler
Paul Selfon
Nieva Valle Concepcion
Timothy Wex(S)
Inez Wilbur
Joseph P. McCormick(S)

Fee Review Committee

Howard E. Ticktin, *Chairman*
J. Keith Cromer, *Vice-Chairman*

William Amoroso
Nicholas Azzato
Jerome Canter
Allan Coleman
Jack Derzavis
Samuel Diener
Charles Epps, Jr.
Henry L. Feffer
Herbert Goldberg
Nicholas E. Gwozdz
Kermit Hanson
Arthur Hustead
Morton Kaufman
Alex R. Kelly
Gerald H. McAteer
Stephen S. Pappas
Robert E. Pumphrey
Linwood J. Rayford, Jr.
Nicholas Smyth
M. Noel Stow

Hospitals and In-Patient Care

John Kenney, *Chairman*
Thomas Curtin, *Vice-Chairman*

Jose M. Antonio
Eugene Clark
Francis D. Cooney
Jerome Epstein
Edward Doyle(S)
Norman Horwitz
Thomas Keliher
Robert Parrott
Ian Spence
John Stapleton
Joseph Swift
Constance S. Pittman(S)
Joseph R. Young

House and Building

Milton Goldman, *Chairman*
Charles Ireland, *Vice-Chairman*

Christopher Bever
Claudine Gay
August Kramm
Arthur Lewis

Legislative

William R. Felts, *Chairman*
Herbert Giffin, *Vice-Chairman*

Harvey Ammerman
Arthur Dick
Paula Kaiser
George N. Polis
Melchior Savarese
Richard Schwartz
Stephen Haas
Joseph Wallace
Warren Brill
James W. Watts
Oscar B. Hunter, Jr.
Robert E. Moran, Jr.
George E. Stevens
Howard Marton

Liaison With Allied Professions

Marvin Fuchs, *Chairman*
Thomas Keliher, *Vice-Chairman*

C. A. Caceres
John Kehoe
Calvin Klopp
Leon Liverett
Mr. Sylvester Zumbrum
Roger Peele
Lawrence Putnam
Massimo Righini
Kirpal Sidhu
Richard Schaengold
Evan Stone
Thomas F. Cullen

Liaison With Medical Schools

Wallace Jensen, *Chairman*

Robert Day
Gregory Berlin(S)
James Feffer
Hemant Joglekar
Thomas Keliher
Marion Mann
Thomas Peery
Frank Talbot
Elbert Phelps
John Rose
Jack Segal
George Schreiner
Jay Shapiro
Bruce Shnider
Alfred Suraci
Don R. Wiesner(S)

Maternal Welfare

Marvin Footer, *Chairman*
Howard Donald, *Vice-Chairman*

Arthur Becker
Hekwan Chung
R. James Clark
William Claytor
Claire Cobb
Edmund Daley
D. A. Dessouky
Julius Epstein
Juan Fraga
James Frawley
David Kushner
Larry McGowan
Donald Payne
Alvin Robinson
Linda Whitby(S)

Medical Bureau

Adolph Friedman, *Chairman*
Agnes McNutt, *Vice-Chairman*

Basdeo Balkissoon
George Boinis
Charles Carroll
Armand Gordon
David H. Kushner
L. M. Liverett
Robert Sherman
Saul Zukerman

Medical Economics Committee

Harvey Ammerman, *Chairman*
Joseph Croft, *Vice-Chairman*

Thomas Arnett
Louis Balla
Lewis Biben
Ray Brown
Max Hurston
Robert T. Dibble
Robert Fisher
Juan Fraga
Bagden Mangasarian
Frederic Meyers
Melba Moore
Frederic Moretti
Norman Paul
Philip Philbin
Leo B. VanHerpe
Fiorello Vicencio

Medicine and Religion Committee

Angelo D'Agostino, *Chairman*
Maxwell Boverman, *Vice-Chairman*

Alice Brigham
Thomas Calhoun
F. Donald Cooney
Edward Fisher
Forest Harris
Nicholas Ionedes
Elizabeth Kahler
Joseph Cantrell
Leonard Maguigad
Joseph Giere
Margaret Nicholson
Anthony Zappala
Glenn Legler
J. Chandler Smith
Robert E. Buckler(S)
Dr. L. R. Ditzen
Chaplain David E. Gregory
Rev. Richard Griffin
Rev. Mike McManus
Rev. Joseph O'Brien
Rev. Robert Olson, Jr.
Rev. Donald Piper
Dr. Thomas Price
Rev. Jo Tartt, Jr.
Chaplain James W. Smith, Jr.
Chaplain Capt. Carl Stevens
Rev. Frank White
Canon Richard Williams
Chaplain Ernest Bruder
Dr. Twor Chikes
Chaplain Richard Dickey
Rabbi Joshua Habberman
Col. Floyd Hecbard
Chaplain Henry Jones

Medicolegal Problems

Jed Pearson, *Chairman*
Alan Crain, *Vice-Chairman*

Marshall Ackerman
William Choisser(S)
Alfred Baer
Louis Balla
Samuel Becker
Charles Carroll
Samuel Diener
Stafford Hawken
Maurice Herzmark
Paula Kaiser
John E. Kelly (D.C. Bar Association)
Allen Lee
Cornelius Murphy
Judson Randolph
John L. Christensen
Harold L. Hirsh
Elliot C. Wilner
Salvatore Fiscina
Daniel Sondheimer

Membership

Ali Moghtader, *Chairman*
Carlos Silva, *Chairman*

Mohan Advani
Samuel Burtoff
Sheldon Gottlieb
Fracis Chucker
Robert Dyer
Bruce Feldman
L. Edward Perraut
Jimmy Head
Hemant Joglekar
James Kehoe
Richard J. Kelly
Douglas Martz
Raymond Noble
Michael E. Jay(S)

Mental Health

Paul Chodoff, *Chairman*
Ranville Clark, *Vice-Chairman*

Clarence Bunge
Arcangelo D'Amore
David Fram
Ricardo Galbis
Haikaz M. Grigorian
Arthur Henderson
Fred Hilkert
Pearl Holly
Warren Johnson
Christine Kehne
Edward Kirby
Maxwell Boverman
Morris Kleinerman
Mark Lawrence
Zigmond Lebensohn
Thayer MacKenzie
Essex Noel, III
Roger Peele
Dorothy Starr
Norman Taub
Edward Weiss
Fred West
Herbert Winston
Leon Yochelson
Jessie Rosenthal(S)

Newsletter

John J. Hughes, *Chairman-Editor*
Jack White, *Vice-Chairman*

James Kehoe
Raymond Scalettar
Paul Schlein
James G. Kane

Occupational Medicine and Health

Charles Humphreys, *Chairman*
Paul Selfon, *Vice-Chairman*

Leonidas A. Ayton
C. W. Brandt
William Chen
S. J. Cosimano
Cornelius P. Frey
George Green
Lewis Klein
Max P. Rogers
Gabe Mirbin(S)
Kirpal S. Sidhu
I. Phillips Frohman

Physical Fitness Committee

Juan Calatayud, *Chairman*
Stanford Lavine, *Vice-Chairman*

Arthur Anderson
Thomas Calhoun
Antonio Canadas
Thomas Carter
S. J. Cosimano
Edmund Daley
Major P. Gladden
Samuel Fox, III
Ernest Martin
Robert Wilkinson, Jr.
Alan Beyer(S)
James Metcalf
Mahmoud Mourad
John Naughton
Alfred Pavot
C. Andrew Rigg
Jorge C. Rios
John Sager
Richard Schwartz
Lowell Weiss
Michael Callahan(S)
Warren W. Pagel(S)

Physician Placement

Alfred J. Suraci, *Chairman*
Arthur Anderson, *Vice-Chairman*

Terry Andrews
Walter Cresswell
Laurence Drell
John Griswold
August Kramm
Uriel Lee
Charles V. Pate
Norman Paul

Provision for Health Services

Louis Gillespie, Jr., *Chairman*
James Watts, *Vice-Chairman*

Thomas Arnett
Barrington Barnes
Paul Cornely
Albert Harden
Arthur Hoyt
Robert R. Huntley
Leroy A. Jackson, Jr.
Mr. John McKinney
Edward Nicklas
Thomas Piemme
Raymond Standard

Public Information and Education

John Keshishian, *Chairman*
Peter Horvath, *Vice-Chairman*

Ceasar Caceres
Fletcher Derrick
Dennis L. Shubert
Michael Halberstam
Jeanna Goffredi(S)
Joseph Pisani
David Kushner
Samuel Loube
Benjamin Manchester
Richard Nicklas
Lois Platt
Nicholas Smyth
James Snyder
Robert Stolar
Richard Whelton
Mervin Zimmerman
Yuill Black

Relative Value Committee

Claudine Gay, *Chairman*
William T. Spence, *Vice-Chairman*

William Amoroso
Robert Dietrich
Sydney Green
Kermit Hanson
David Berler
William Jaffurs
Howard Katzman
Herbert McKnight
Vernon Martens
James R. Snyder
George Tievsky
Harold M. Silver

Ruffin and Other Bequest Funds

James McFarland, Jr., *Chairman*

Claudine Gay
Carlos Silva
Duane Richtmeyer
Robert F. Dyer

Smoking and Chest Diseases

Russell Tilley, *Chairman*
Horace Custis, Jr., *Vice-Chairman*

Teofanes Carreno
E. Raymond Fenton
Sol Katz
Uriel Lee
Oscar Legault
Ivan Magal
Bernard Grand
Armando Miranda
Robert B. W. Smith
Paul Snow
Mohammed R. Taleghani
Lowell Weiss
Lennox S. Westney
Asher D. Rabinowitz(S)

Special Awards

Henry Ecker, *Chairman*

Robert Coffey
Seymour Alpert
K. A. Hardin
Wallace Yater

Traffic

Herbert Gates, *Chairman*
Samuel Bullock, *Vice-Chairman*

Francis Blackwell
Maurice Casey
Kenneth Cho
Milton Cobey
Thayer MacKenzie
David Pendergrast
G. Victor Simpson
Harold Yates
William Kurstin

Utilization Committee

Wesley M. Oler, *Chairman*
James Foster, *Vice-Chairman*

Mary Lou Barker
Henry Bell
Thomas Curtin
Monis Dachman
William Feller
Robert Greenfield
Daniel Y. Patterson
Robert Havell
Norman H. Horwitz
Morris Kleinerman
Douglas Martz
Albert Miele
Vinod R. Mody
Daniel Sondheimer
Louis E. Perraut
John W. Price
Massimo Righini
Paul Schlein
Franz-Joseph Weber
Mr. Richard Dodson
  Medical Service of D.C.
Mr. James Bryson
  Health Insurance Council
Mr. Darrell A. Spencer
  Connecticut General Life
  Insurance Company

Liaison With Foreign Medical Schools and Medical Organizations

Caro Luhrs, *Chairman*
Cyril Crocker, *Vice Chairman*

Malcom Martin
Juan Calatayud
Sander Lachman
Henry Feffer

Rehabilitation Committee

Moe Weiss, *Chairman*
Francis L. Wenger, *Vice-Chairman*

William P. Argy, Sr.
Kenneth Cho
James Duke
Eaton Gashi
Barrett Goldstein
Lawrence Klein
Margaret Kenrick
Siu Wah Lee
John Naughton
Alfred Pavot
Irene Tamagna
Arthur West

ANNUAL BUSINESS MEETING
November 15, 1972

Agenda

1. Call to Order—Darrell C. Crain, M.D.
2. Reports of the Officers
3. Report of the Nominating Committee
4. Introduction of New Officers
5. Special Awards
6. Society Business
    a. Abortion Guidelines
    b. Medical Foundation
    c. Health Maintenance Organizations
7. New Business
8. Adjournment

In Memoriam

Bachrach, Louis	Active	June 21, 1972
Brooks, Richmond	Life	April 15, 1972
Calver, George	Honorary	February 27, 1972
Edison, Thomas	Associate	November 28, 1971
Eichenlaub, Frank	Active	February 13, 1972
Feldstein, Percy	Associate	August 16, 1972
Freeman, Walter	Life	May 31, 1972
Gordon, Gerhart	Active	April 23, 1972
Greear, James N.	Special	November 9, 1971
Jackson, Caroline	Special	April 8, 1972
Kittredge, Elizabeth	Life	July 23, 1972
Knowlton, Don	Life	April 8, 1972
Leibell, Casimir	Life	August 8, 1972
Moran, Robert	Life	July 22, 1972
O'Donnell, Roger	Special	August 29, 1972
Parks, John	Active	July 5, 1972
Roggenkamp, Oswald	Associate	July 20, 1972
Shea, Frank	Special	September 1, 1972
Short, Eleanor	Active	January 20, 1972
Stanbro, William	Active	June 23, 1972
Stevenson, Leland	Life	September 14, 1972
Strong, William	Special	May 13, 1972
Szollosi, Etienne	Associate	August 10, 1972
Walker, Claude	Active	January 12, 1972
Weinstein, Howard	Active	April 23, 1972
Wissler, James	Special	May 5, 1972

Report of the Chairman—Executive Board

It has been a privilege to serve as Chairman of the Executive Board during a year in which, under the leadership of an able and energetic President, our Society has played an ever greater role in local and national medical affairs. The Board has been very busy throughout the year. Only a few of its actions will be described in this report.

Reprimand Action Against Dr. Milan Vuitch

Upon the recommendation of the Grievance Committee, ably chaired by Dr. Wesley Oler, the Executive Board, after a hearing with Dr. Vuitch, decided to reprimand him for disregard of the law related to abortions. Dr. Vuitch was convicted of criminal abortion in the District of Columbia only to have that conviction reversed by a higher court because the District law was considered too vague. This law was later upheld by the Court of Appeals which, in the same action, indicated that in the future the prosecution must prove that the abortion performed was *not* necessary to preserve the life or health of the mother. Dr. Vuitch was convicted of the same offense in Maryland courts. Later he succeeded in having the Maryland law declared unconstitutional by a federal court.

Following his reprimand, Dr. Vuitch exercised his right to demand a special meeting of the membership to hear his appeal. In this meeting the action of the Executive Board was upheld by the membership. Dr. Vuitch then appealed to the Judicial Council of the American Medical Association. That Council also upheld the reprimand action of the Board.

Incorporation

Having worked diligently toward the passage of a law to enable physicians to incorporate, the Society approved a symposium which was programmed and conducted by Dr. Harvey Ammerman and his Committee on Medical Economics. The new incorporation law has been of considerable aid to certain physicians and groups of physicians engaged in the private practice of medicine.

Professional Liability

The Board approved a recommendation of the Committee on Medical Economics under the Chairmanship of Dr. Harvey Ammerman to conduct a poll by which to determine the membership's desire for a group policy for professional liability insurance. The Medical Economics Committee has since been exploring various possibilities in order to secure the best liability coverage for Medical Society members and will make its recommendations shortly.

Gun Control Legislation

The Committee on Mental Health under the Chairmanship of Dr. Paul Chodoff recommended to the Executive Board that the membership be polled on the subject of gun control legislation. This recommendation was approved. The returns from the questionnaire showed that the members were highly in favor of gun control. Consequently, the Board approved a resolution to be taken to the House of Delegates of the AMA in June by Dr. Camalier and Dr. Hughes. The House of Delegates by a large majority voted against the resolution. Since this action, the Board has given the Chairman of the Mental Health Committee permission to write to the Council on Mental Health of the AMA asking that it survey various State Mental Health Committees on the question of gun control.

Liaison with Commission on Licensure

For several years our Society has been attempting to effect changes in the Healing Arts Law of the District of Columbia. Although we have not been successful in rewriting the law, we have been able to exert considerably more influence on the Commission on Licensure through the efforts of the Immediate Past President, Dr. Korengold, and the more recent efforts of the President, Dr. Crain. The Board has approved the appointment of a Liaison Committee consisting of the President, President-Elect and Executive Director to work with the Commission on Licensure. Dr. Crain has met with members of the Commission and has developed far more cooperation with it than at any time in recent years. It is hoped that eventually permanent changes in the Healing Arts Law will be brought about to allow greater participation in the work of the Commission by practicing physicians.

Continuing Education

The Board approved a recommendation of the Continuing Education Committee to conduct a seminar on drug abuse. A series of four lectures were held beginning in May.

Dr. Raymond Holden

Our distinguished Past President and current member of the Board of Trustees of the AMA, Dr. Raymond Holden, will seek to be elected as President-Elect of the AMA next June. The Board enthusiastically approved the endorsement and support of the candidacy of Dr. Holden during the forthcoming year. The Society plans to work toward his election in a number of different ways to be announced.

Medical Foundation

Medical Foundations for utilization review by physicians and for the delivery of health care have been appearing rapidly throughout the United States. The Executive Board endorsed and approved the creation of a Medical Foundation for the Washington area and authorized the President to move forward with Articles of Incorporation and Bylaws. A representative Committee at Large, appointed by the President, has held several meetings throughout the summer months. Articles of Incorporation have been formulated and the Bylaws of the Foundation are in the process of being finalized. The creation of the Medical Foundation represents a great deal of hard work by President Crain and the Committee at Large and should keep Washington area medicine in the mainstream of medical progress in the country.

Abortion Guidelines

The Committee on Maternal Welfare under the Chairmanship of Dr. Marvin Footer, with the guidance of the President, has worked throughout the year not only independently but also in cooperation with the Department of Human Resources to formulate guidelines for performing abortions outside of hospital facilities. These guidelines are to be circulated to the Society before the end of the year, with a request that our members abide by them.

Continuing Education

Upon the recommendation of the Committee on Continuing Education, chaired by Dr. Jay Shapiro, the Board approved a program of reeducation, providing credit hours to members who participate. The movement toward some form of continuing education is progressing steadily throughout the country. In two states, Maryland and Nevada, physicians are relicensed at regular intervals only after showing proof of attendance at meetings or seminars, writing of medical papers, medical teaching, etc. It is the wish of the Committee and of the Executive Board that the plan should be started here on a voluntary basis, with a provision that it become mandatory at a later date.

Medical Annals of the District of Columbia

After forty-two years of service to the Society and more specifically to the MEDICAL ANNALS, the Board resolved to name Dr. Wallace Yater Editor Emeritus upon his retirement from active editorship of the ANNALS on January 1, 1973. Dr. Yater's contributions to our Society are well known. A testimonial dinner celebrating this occasion was held in September at which time many of his friends and colleagues paid tribute to him.

Finale

Many thanks to all the Society members and to the Executive Board for making 1972 a banner year in our history!

Report of the Board of Credentials

Compared to last year's report there has been a sizeable increase this year in the number of applicants for membership in the Society. During the past twelve months there were 253 applicants interviewed for membership. Of this total, 195 were for Active membership; 46 for Associate membership; and 32 for Resident-Intern membership. Twenty-nine (29) student applicants were processed and approved.

This year the Board streamlined the process of verification of the application and thereby reduced the duration of time an applicant would have to spend with the Board members. This has helped to ease the workload considerably.

The following statistics reflects the attrition of Society membership this year: 48 resignations; 35 members dropped from the Society's rolls due to nonpayment of dues; and 26 deceased members. Of the 48 resignations, 25 were Active members, 21 Associate members, and 2 Resident-Intern members. The largest single contributing factor affecting resignations was due to physicians moving their offices to another state. Also during the same time period, there were a total of 78 transfers in membership approved by the Board of Credentials. Forty (40) involved the transfer of Active members to Associate members; 18 from Active to Special; and 18 other transfers.

The membership of the Society as of October 1, 1972, is as follows:

Active	1,735
Associate	749
Resident-Intern	45
Special	39
Life	178
Honorary	32
Student	74
TOTAL	2,852

The total membership of the Society during the last ten years is as follows:

Year	Active Membership	Total Membership
1972	1,735	2,852
1971	1,661	2,719
1970	1,642	2,596
1969	1,651	2,513
1968	1,640	2,497
1967	1,595	2,440
1966	1,555	2,444
1965	1,518	2,421
1964	1,535	2,313
1963	1,532	2,275

Eugene Clark, M.D., *Chairman*
Charles Ireland, M.D.
William J. Jaffurs, M.D.
Kenneth McCoy, M.D.
Dennis Hand, M.D.
Edward Pacious, M.D.

Respectfully submitted,
John Lynch, M.D.
John Marbury, M.D.
William Funderburk, M.D.
John Latimer, M.D.
Paul Kiernan, M.D.

medical annals of the district of columbia

vol. 42 no. 2 february 1973

Report of the Executive Director

The tempo of activity within the Society during the last twelve months has remained at the same level which I reported a year ago. This activity is a manifestation of the many problems and forces which face the medical profession today.

This past year several new committees were created to deal with specific health problems. Committees on Provision of Health Services, Medical Care in Correctional Institutions, and Medical Foundation are examples of newly created committees. Also, through the efforts of President Dr. Korengold in 1971, and President Dr. Crain in 1972, the Society has been successful in establishing a Liaison Committee with the Commission on Licensure of the District of Columbia.

There are presently forty-six Committees of the Society, not including 32 Sections. On an average, there are two committee meetings every day or evening. To use an old cliche, your Society is alive and active, and all credit is due to the dedicated work of the Officers, Committee Chairmen, and Committee Members.

During 1971 a number of changes were made in the organization and operation of the administrative staff. I feel confident in reporting at this time that these changes have brought about an effective management team, fully capable of the responsibility of an operation with a two million dollar cash flow.

Early in 1972, Mr. Doug Torrence joined the staff to accept the management of Building Services, Medical Bureau, and Membership Services. The other three divisions of the Society's operation are managed by Mr. Mike Eason: Accounting Services, including Computer Programs and Insurance Programs; Miss Beth Custer: Conference Services, including Scientific Assembly and Secretarial Services; and Miss Judy Perruso: Publications.

This past year has seen a number of changes in the administration of the Regional Medical Programs. In conjunction with these changes, the Executive Director and his Assistants have absorbed a number of administrative functions which, prior to the changes, were handled by the Core Staff of R.M.P. These changes have resulted in a closer day-to-day liaison with the Coordinator and his staff.

A significant goal was reached this past summer with the conversion to computers of all accounting and membership records. This Society is one of approximately six state societies which have computerized its membership records in coordination with that of the American Medical Association. The computerization of our accounting system, especially in the area of cost control, will result in improved information retrieval and financial management.

In connection with the financial position of the Society, I am pleased to report that last year's serious deficit picture has been reversed. It is expected that this fiscal year will show a slight surplus of income which, of course, will be plowed into next year's operation. The budget for next year, however, will show a slight deficit for 1973 operations. It is hoped that through the course of the year this deficit may be avoided, in spite of the fact that the cost of doing business continues to rise.

This is the conclusion of my second year with the Society. I want to assure you that it has been a privilege to serve as your Executive Director; and it has been a greater privilege to have worked with President Crain, Chairman of the Board McCune, and all the other Officers.

Report of the Nominating Committee

The Committee met on Tuesday, September 19, 1972, in the Medical Society Building, at which time the following slate of candidates, for the offices indicated, was selected by closed ballot. In accordance with the bylaws of the Society, this ballot is hereby published to the voting membership.

President-Elect (73)	Clifton R. Gruver, M.D.
Member, Executive Board (73)	James Boland, M.D.
Member, Executive Board (74)	Jack White, M.D.
Member, Executive Board (75)	Edwin Parker, M.D.
Member, Board of Credentials (75)	Haikaz M. Grigorian, M.D.
Member, Board of Credentials (75)	Margaret Kenrick, M.D.
Member, Board of Credentials (75)	Robert E. Pumphrey, M.D.
Member, Board of Credentials (75)	Cleveland E. Smith, M.D.
Delegate to AMA (74)	C. Willard Camalier, M.D.
Alternate Delegate to AMA (74)	Raymond Scalettar, M.D.
Board of Trustees of Group Hospitalization (78)	Harry Zehner, M.D.
Board of Trustees of Medical Service of D.C. (76)	Jack Kleh, M.D.
Board of Trustees of Medical Service of D.C. (76)	Howard Ticktin, M.D.

Nominating Committee—1972

Marvin C. Korengold, M.D., Chairman
Jerome Canter, M.D.
James Fitzgerald, M.D.
James Walsh, M.D.
Frank Ashburn, M.D.
Charles Coakley, M.D.
James McFarland, M.D.
Leon Yochelson, M.D.

Proposed Budget—1973

Society Income	
Active Dues	$244,630.00
Associate Dues	29,960.00
Resident-Intern Dues	680.00
Student Dues	480.00
Scientific Assembly Income	34,100.00
Regional Medical Program Reimbursement	104,000.00
Publication Income	69,020.00
Medical Bureau Income	305,900.00
Building Space Receipts and Reimbursement	114,760.00
Other Income (Interest, AMA Rebate, Services)	27,400.00
	$930,930.00
Society Expenses	
Administrative Expenses	$210,810.00
General Operations Expense	79,120.00
Special Membership and Committee Activity	80,570.00
Scientific Assembly Expense	34,960.00
Membership Department Expense	20,590.00
Publications Expense	77,530.00
Medical Bureau Expense	313,710.00
Building Operational Expense	93,450.00
Mortgage Principal Curtailment	25,000.00
Total Society Expenditures	$935,740.00
Net Results From All Functions	$(4,810.00)

medical annals of the district of columbia

vol. 42 no. 2 february 1973

Report of the Woman's Auxiliary

It is indeed an honor to report to the Members of the Medical Society of the District of Columbia the work the Woman's Auxiliary is and has been doing for the fiscal year 1972–73.

Our Auxiliary year began in July with our first meeting held in September. Thus our year is just beginning, and it has been a great one.

In September the Annual Meeting was held at Normandy Farms. The guest speakers were Dr. Darrell C. Crain, President of the Society, and Mrs. Norman Gardner, Eastern Regional Vice President of the Woman's Auxiliary to the AMA. Dr. Crain brought greetings from the Medical Society and urged us to all attend the Greenbrier meeting. Mrs. Gardner stated that there are nearly 80,000 Auxiliary members, in 1,100 counties and hoped that we are women who want to be better informed in areas of economics, social changes, and politics as they affect and are affected by medical practice.

In October we canceled our regular meeting so that Auxiliary members would be free to attend the Greenbrier. As you know, the turnout was superb. Mrs. Harold Yates, AMA-ERF Chairman; Mrs. Charles Pate, Eastern Regional AMA-ERF Chairman; and I set up our "Traveling Gift Shop." During our one and one-half day sale, we grossed $680.00. We thank you for your generous support.

The American Medical Association-Education and Research Foundation is our major concern. This year National has requested that our goal be $10.00 per person so that we can better support the AMA Loan Fund program for medical students, interns, residents, and medical schools. We are well on our way. As of this date we have netted approximately $15,000.00. This has been achieved by our "Traveling Gift Shop" and the selling of raffle tickets for an "Instant Cocktail Party" under the direction of our Ways and Means Chairman, Mrs. Herbert Schoenfeld. The Medical Society has generously supported all of our endeavors. Our final fund raising benefit will be on March 3, 1973, in the form of a Mardi Gras at the Bethesda Country Club to support not only AMA-ERF but also our Nursing Scholarship Fund.

The Auxiliary International Health Chairman, Mrs. Anthony Zappala, is working on Project SKIP–Scholarship for Kids of International Physicians. Many outstanding doctors who assume positions in small mission hospitals or clinics need help with the education of their children, particularly where no educational facilities are immediately available. For $30.00 per month an international physician's child may be adopted and receive the benefit of schooling for one year.

Our Bylaws Chairman, Mrs. Seamus Nunan, is working on revisions of our Bylaws. All Doctors' wives are welcomed to participate in the Auxiliary. A change in our Bylaws will make it easier for the wives of all doctors who are members of the Medical Society of D.C. to join our efforts.

Mrs. John L. Fox
President, 1972-73

Nominations to the Health Foundation

The Health Foundation's Bylaws stipulate that the Board of Directors (eleven) be named by the Medical Society. The Board must include the Society's President, President-Elect, Secretary-Treasurer, three other members of the Society and five additional members including a dentist, a pharmacist, and a registered nurse. It is recommended that the following be approved as members of the Health Foundation's Board of Directors for one year beginning January 1, 1973.

President–MSDC
President-Elect-MSDC
Secretary-Treasurer-MSDC
Mr. John McHugh
Miss Grace Mathews
Mrs. Jane Yates
Irving M. Rothstein, D.D.S.
Marvin C. Korengold, M.D.
Henry D. Ecker, M.D.
Erman W. Edgecombe, M.D.
Mr. Renal Camalier

Report of the Delegates on the AMA Clinical Convention

The 26th Clinical Convention of the American Medical Association was held in Cincinnati, Ohio, November 26 through 29, 1972.

The House of Delegates met for nine hours, and acted upon 59 reports and 65 resolutions.

The "hottest issue" was consideration of the posture of the AMA regarding HR-1 and PSRO. Recognizing that the Association has opposed the legislation, the House voted to assume a position of leadership and influence, since HR-1 was enacted. An AMA advisory committee on PSRO will be promptly created by the Board of Trustees. It will include members of the Board, and the Council on Medical Service—others may be included at the discretion of the Board. This committee will seek to "provide a dominant role of leadership in the implementation of the PSRO program to assure that the best interests of the public and the profession are preserved." Over 10 specific areas of responsibility of the committee were defined: to include input from the medical profession in development of the rules and regulations which will govern the PSRO program—to assist State and County Associations in developing PSRO's—to aid in defining appropriate geographic boundaries for PSRO's—and to monitor (and report to each future House session) the effect of PSRO on medical care.

AMA President, Carl A. Hoffman, identified as major national health problems, the need to protect Americans from financial ruin due to catastrophic illness and the maldistribution of physicians as it affects the inner city and rural areas. He suggested a required-practice proposal under which a medical student would repay a government subsidized education by serving three or four years in a medically deprived area. He further stated that creation of adequate catastrophic health insurance should not be as "insoluble" a problem as represented by the insurance industry.

As urged by the House in previous sessions, the Board of Trustees implemented several areas of fiscal restraint. Among these were the termination of four councils and six committees, and cessation of AMA specialty journals as a membership benefit (they will continue to be available by subscription).

"Prism," a new AMA socioeconomic publication, will be sent as a membership benefit early in 1973.

The House members balloted to indicate their preference for terms of the Board of Trustees. A majority voted to allow a maximum of two three-year terms, rather than the present three term maximum.

Twenty-three state and many local societies have established committees on the health care of the poor since this was recommended by the House in 1971. The Council on Medical Service urged and the House endorsed further increase in these efforts at the local level.

The House urged organized medicine to continue and increase its assistance to the rapidly increasing number of "Free Clinics" in the nation (over 200 at present).

The Delegates urged that operating standards of the American Association of Blood Banks and the American Red Cross be recognized and accepted by a Federal Panel on Blood Banking, and that physicians be represented on any national panel.

Dr. John Mather of the University of Maryland Hospital was named as the first Intern-Resident member of the Council on Long Range Planning and Development—which council was specifically expanded to allow the appointment of an Intern-Resident member.

The House plans to add an Intern-Resident member to the Council on Medical Service and the Council on Medical Education—this action is expected at the 1973 Annual Meeting.

George Blatti, a senior student from the University of Minnesota Medical School, was seated as the first voting student AMA Delegate. Annual dues for student AMA members were set at $15.00.

The AMA sought and has obtained revision of an Internal Revenue Service ruling which barred withdrawal of voluntary Keogh contributions prior to disability or age 59½. This revision will allow withdrawal of such contributions made prior to March 6, 1972.

Bob Hope will receive the Layman's Citation for Distinguished Service at the Annual Meeting in 1973. Mr. Hope has contributed almost 1.5 million dollars to the Eisenhower Medical

Center in California, and has raised another 3.5 million for the Center.

The Council on Long Range Planning and Development reported on its several regional membership hearings, and announced acceptance of the Medical Society of the District of Columbia and the Medical Society of Maryland's invitation to hold a hearing in the District of Columbia in early March of 1972. The Council will hear oral or written statements from individual physicians, from spokesmen of medical societies or other medical organizations, and from medical students.

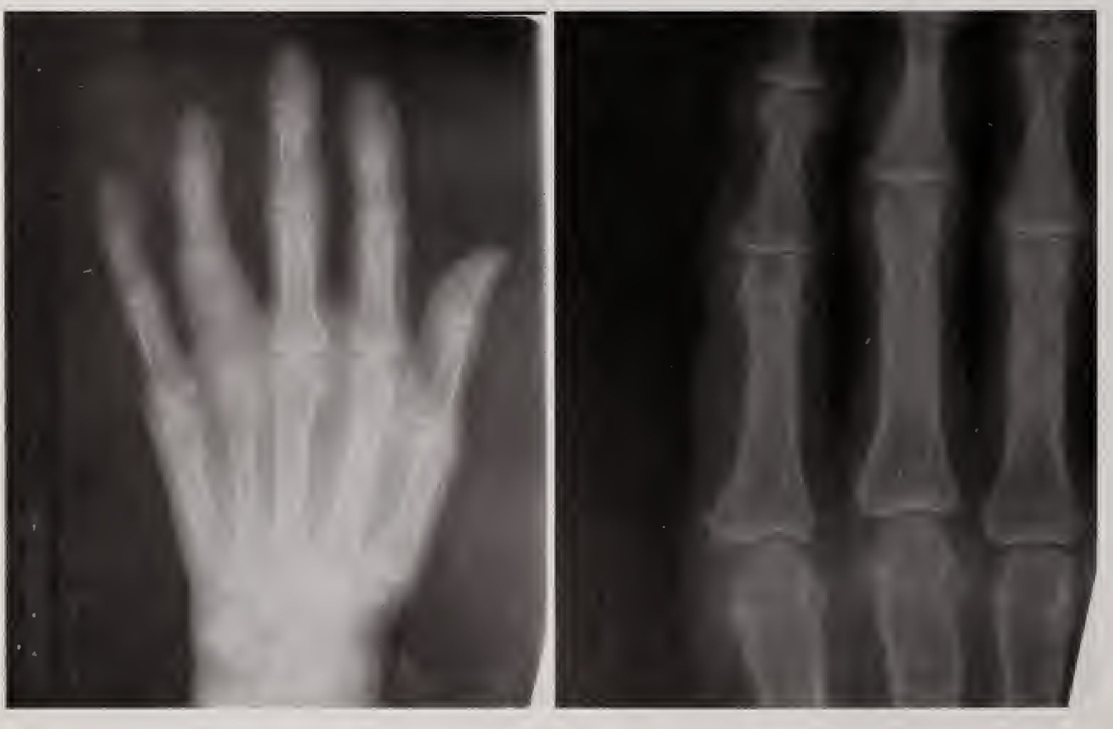
The House of Delegates heard disturbing testimony in June of 1972 regarding the claims practices of Aetna Life and Casualty Company. Report J of the Council on Medical Service at the Cincinnati meeting gave an optimistic report of its negotiations and tentative agreements with Aetna in the past six months. However, the House heard much testimony indicating that, at least in some areas, the objectionable practices of Aetna remain in effect. Accordingly, the House directed the Council on Medical Service to collect and accumulate data as presented by individual physicians, as well as local and state societies regarding the claims practices of Aetna, and to report this information to the House at the Annual Session in 1973.

John J. Hughes, M.D., *Delegate*
C. Willard Camalier, Jr., M.D., *Delegate*

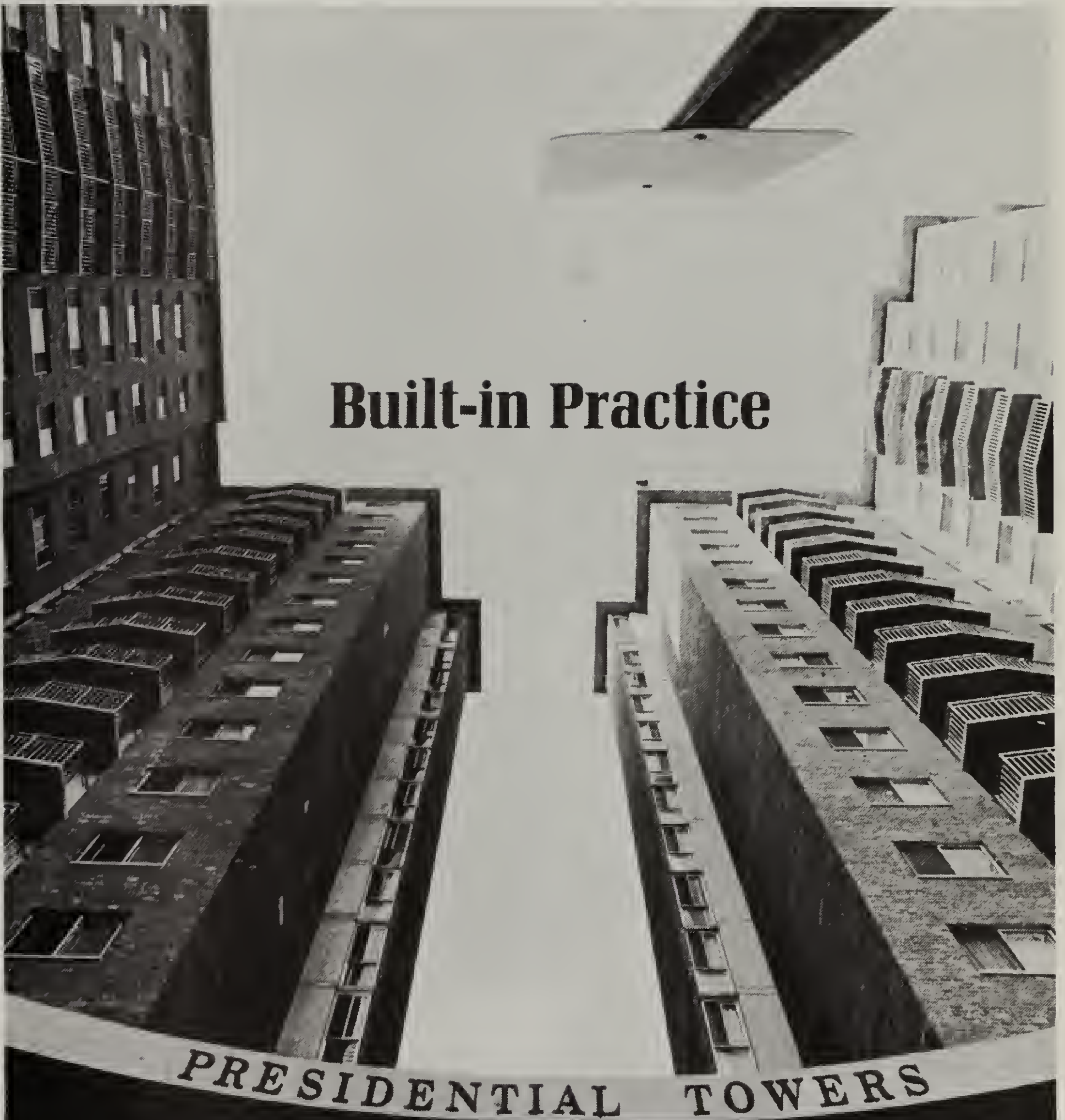
THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center

A 67 year old housewife presented with a history of lethargy and nausea. She complained of bone pain ("they are tender and hurting") and she called attention to swelling of the back of her right hand.



(For diagnosis see page 101)



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7534 Annapolis Road (Lanham)	577-7282
Waldorf Mall, Waldorf, Md.	843-6331
Glenmont Shopping Center, Georgia Ave. & Layhill Rd. (Wheaton)	942-2300
Prospect Plaza Shopping Center, South Jefferson St., Routes 340 & 15, Frederick, Md.	(301)663-4861
Park and Shop Shopping Center, US #1 by-pass at College Gate stoplight, Fredericksburg, Va.	(703)373-4607

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

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Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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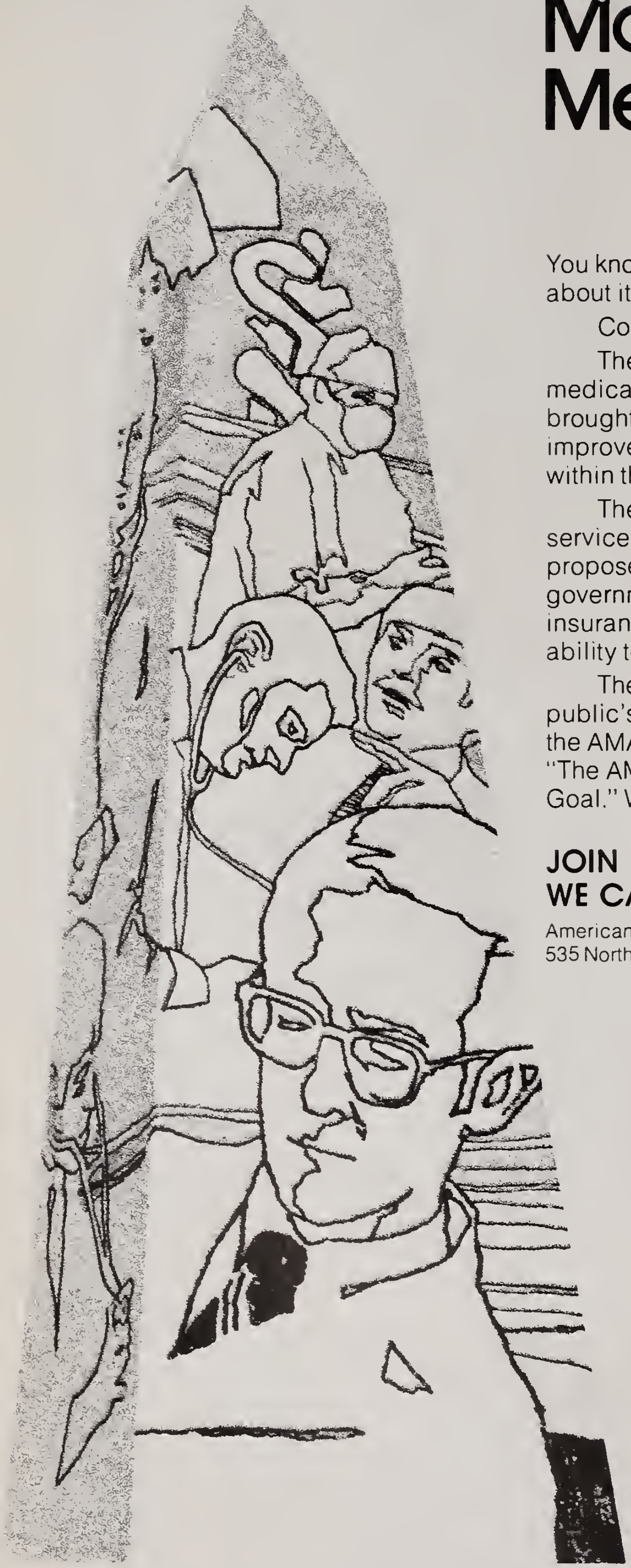

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OBITUSSIN-DM®	●	●		●		●
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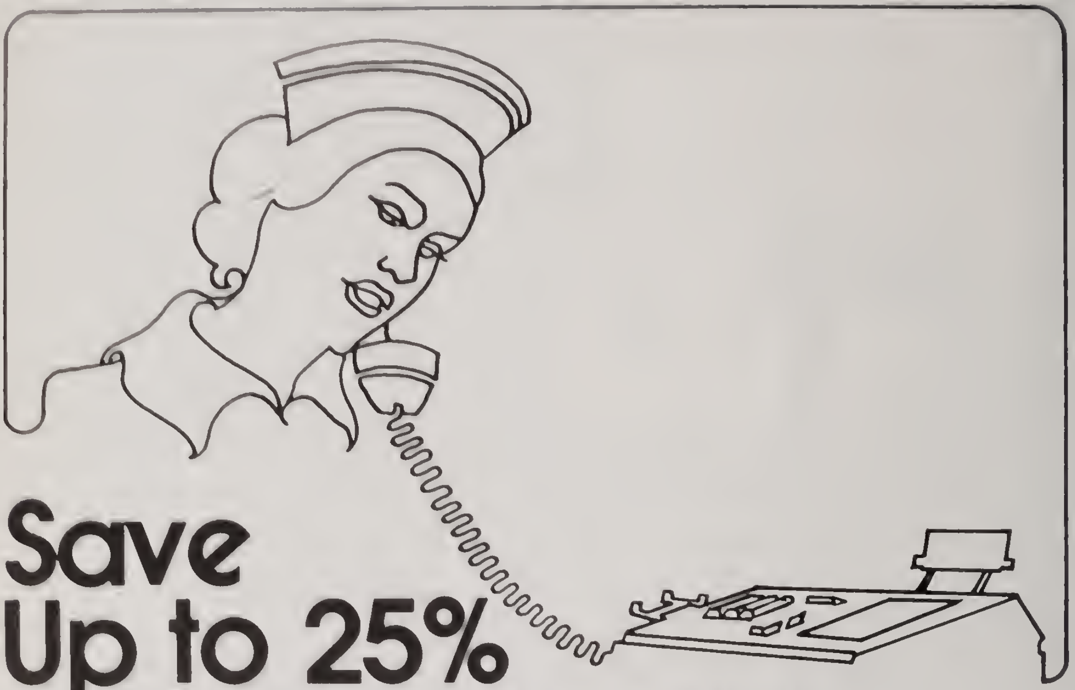

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MEDICO-LEGAL REPORT

Surgeon's Liability for Nurse's Negligence—The "Lent Servant"

A patient has asked her surgeon to remove a skin lesion on her leg while she is anesthetized for an unrelated operation. He agrees and directs a hospital nurse to set up a "Bovie" electrosurgical machine, which the nurse does while the surgeon is not in attendance. When the equipment has been readied, the surgeon enters the operating room and proceeds with the surgery. It is a rather simple operation, and the surgeon anticipates few problems. However, because the nurse negligently misplaced an electrode, severe burns to the patient's leg result.

Both the machine and the nurse were supplied by the hospital. The nurse had been trained by the hospital to prepare "Bovie" machines for operations. On this occasion, as on many others, the surgeon did not feel any need to supervise the nurse's work. Nevertheless, the patient is now in court claiming that the nurse's negligence is attributable to the surgeon under the doctrine of *respondeat superior*; that is, the patient argues that the nurse was an employee, or at least a "lent servant," of the surgeon and that he must answer for her negligence.

Should the patient recover from the surgeon on these facts?

In Maryland, Virginia and the District of Columbia, the answer at present is that the patient probably cannot recover from the surgeon. The answer is not as clear in many other jurisdictions. Moreover, even in this area, recovery may well have been allowed in years gone by. Recent decisions may not put to rest all of the doubts a surgeon may have in a situation such as this, since almost all of the cases in the area involve highly particularized fact situations from which juries are relatively free to draw inferences either favorable or unfavorable to the surgeon. But the cases definitely exhibit a growing feeling among judges that the doctrine of *respondeat superior* should not be construed too broadly. It is believed that a doctor's liability for the acts of so-called "lent servants" is in fact becoming more difficult to establish even in this day and age of an increasing number of malpractice suits. Hence, unless a patient can demonstrate at least some basis for imposing liability on a surgeon on the theory of *respondeat superior*, a judge may never allow the case to go to the jury.

The hypothetical fact situation set forth above is based on a fairly recent District of Columbia case. While independent evidence of the surgeon's own negligence sustained the right of the patient to have the jury hear her case, the court avoided coming to any conclusion on the question of whether the evidence supported a legal finding that the nurse functioned as the surgeon's employee. It apparently did not believe that the plaintiff's evidence on the matter was too convincing.

There are still many circumstances in which an agency relationship between a surgeon and a "lent servant" may be established. In *Whitfield v. Whittaker Memorial Hospital*, a recent Virginia decision, the evidence of temporary

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agency was held sufficient to go to the jury. There, the patient had died as a result of the negligent administration of an anesthetic by a hospital employee during an operation. Even if the surgeon were not exercising actual control over the nurse's work, he was nevertheless in a position to do so and unquestionably had the right to do so. This distinguished the case from others where the anesthesiologist was another doctor over whom the surgeon had no apparent control. Evidence that the surgeon selected the kind of anesthetic to be administered, told the nurse when to begin and could stop her at any time was sufficient to establish the degree of control and supervision necessary to allow the question of agency to go to the jury. As a matter of agency law, the decision appears sound. If the distinction is sound as a practical matter, however, one cannot help concluding that a surgeon would be wise to insist upon another doctor administering the anesthetic rather than a nurse, no matter how competent the latter may be. That this may be unnecessary and impractical in many situations, in terms of precaution, seems not to be recognized. So one may question the theoretical basis for the distinction as far as it relates to establishing an agency relationship in one case but not in another.

The Maryland rule on the subject is well settled. A surgeon is not held responsible for the negligence of nurses and interns for pre- or post-operative care and treatment if he does not know of and is not privy to such negligence and if it is not discoverable by him in the exercise of ordinary care. A Connecticut court has followed the Maryland rule in holding that there was no evidence of agency even where the patient's injury resulted from a negligently administered pre-operative injection which was directly related to the patient's preparation for surgery. The court was unwilling to infer that the surgeon had supplanted the hospital as master and supervisor over the negligent nurse even though the doctor might have known the injections would be given and could have supervised the nurse in making them. It was felt that this was simply not the type of act that necessitated a doctor's supervision.

Several explanations may be offered why courts are more hesitant to find an agency relationship between surgeons and so-called "lent servants" today. First, the general increase in competence and training of hospital employees diminishes the need for a surgeon to supervise everything done to and for his patient. Second, and perhaps as a corollary, the sophistication of some hospital equipment may preclude a surgeon from becoming as familiar and as competent with its use as someone who has been specifically trained in its use. Finally, as a public policy matter, there may be less need for courts to go such great lengths in attaching *respondeat superior* liability to a surgeon. A very recent Oregon decision suggests this was once the case because most hospitals had charitable immunity, thus depriving a plaintiff from recovering from anyone with the ability to pay unless he was permitted to sue the surgeon. Now that charitable immunity for hospitals has been abolished in many places [and they have begun to insure themselves], the policy argument for shifting the potential of liability onto the doctor in order that the patient be allowed to collect from at least someone has lost its impact.

At what point in the operating procedure, then, should a surgeon become aware of possible liability for the negligent acts of a hospital nurse? If the case law offers any answer, it is that the surgeon should bear no responsibility for those acts which are preparatory to an operation and which are performed as a matter of hospital routine on all patients. In such case, the surgeon would rarely have special knowledge of what acts are being done by a nurse or other staff member and, obviously, would be exercising no actual supervision over them. And even if the same nurse later comes under the surgeon's special control and supervision in the operating room, the lack of any relationship with the surgeon prior to that time should remain unaffected thereby. This, at least, was the rule of law followed in the recent District of Columbia case decision, where the court stated that "the fact that the nurse is under the doctor's supervision and acts under his orders as to some matters does not make her his agent for all purposes." This evidently means that a court will consider the existence of any alleged agency relationship act-by-act rather than find that a nurse is a "lent servant" for all purposes beginning at a particular point in time.

Doctors will hardly rejoice knowing that a patient's case in this area of liability is somewhat more difficult to establish today in some jurisdictions, because the fact is that it is still relatively easy to establish a temporary agency relationship between a doctor and a hospital nurse. Doctors will still be on their guard to ascertain whether a nurse they may never have seen before is competent in her work. And, obviously, there will be situations when time does not allow any investigation at all.

ANDREW MACDONALD

Edited by Stefan F. Tucker of Arent, Fox, Kintner, Plotkin and Kahn, Washington, D. C.

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Associate

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THE VIEW BOX

(from page 86)

DIAGNOSIS: Hyperparathyroidism (secondary hyperparathyroidism due to chronic renal disease)

The radiograph of the hand shows subperiosteal bone resorption, most marked along the radial aspect of the middle phalanx. There is loss of cortical definition and a lace-like appearance. In the proximal phalanx of the 4th digit is a "bubbly" lesion with expansion of the bone, thinning of the cortex and without calcified matrix.

Approximately 40% of patients with hyperparathyroidism, either secondary or primary, develop bone changes as demonstrated in these radiographs. Similar changes can often be seen on the medial aspect of the proximal tibia and distal ends of the clavicles. The changes in the proximal phalanx of the 4th digit are consistent with a "brown" tumor. Radiographically, the bone changes in primary and secondary hyperparathyroidism are identical.

Edited by Gunter J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

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KENNETH C. ULLMAN, M.D. Office: Georgetown University Hospital. Born in Baltimore, Maryland. Medical degree: University of Maryland, 1969. Specialty: Psychiatry.

Student

Georgetown University. Freshmen: Steven A. Aurecchia, Alan H. Beyer, Robert E. Buckler, Michael P. Carroll, Feliciano Chuy, Sean M. Dwyer, Robert S. Goodwin, Peter G. Perakos, John E. Phelps, Luis E. Sanz, Dein M. Shapiro, James S. Yoshikawa.

George Washington University. Freshmen: Steven A. Burka, Brian Zimmerman. Sophomore: Dennis L. Shubert.

Changes in Membership

Transfers

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Resident-Intern to Active: Raymond Lloyd, M.D., Siegmund Teichman, M.D.

Active to Associate: Peter Colevas, M.D., Melvin W. Sandmeyer, M.D., Donald Walters, M.D.

Associate to Special: Lester Harris, M.D.

Reinstatement

Active: Albert A. Greenfield, M.D.

Resignations

Active: Genieann Patton, M.D.

Associate: John D. Archer, M.D., Oscar Lavine, M.D., Jack J. Levin, M.D., Harry B. Orleans, M.D.

book REVIEWS

Plastic and Reconstructive Surgery, 3rd edition. HANS MAY, M.D., F.A.C.S. Price, $50.00. Pp. 1255, with 916 illustrations. Philadelphia: F. A. Davis Company, 1971.

This is an attractive volume, printed on good paper with excellent reproductions of the voluminous illustrations. In the main, this third edition is a worthy successor to the previous editions. The general format follows that of previous editions and is divided into five sections, the first four of which are discussions of the various aspects of the field of Reconstructive Surgery, including the basics of wound healing, types of sutures utilized, preoperative preparations and surgical treatment from the simple to the more complicated pathology. In the last section, clinical case studies with detailed descriptions, photographs and method of repair are gathered, thereby enhancing the value of the text material.

We have all seen such poor and devastating results from the use of "Small Deep Skin Grafts" illustrated on page 44, that I wish it had been completely omitted, but perhaps it was shown only for sake of completion, for Doctor May certainly does not recommend its use.

Burns are of particular import and for practical purposes are divided into the immediate treatment consisting of combating shock, toxemia and infection and late treatment consisting of combating malnutrition, resurfacing with skin grafts and rehabilitation.

His discussion of repair of facial paralysis is complete and he leans toward the two stage repair devised by Ragnell and using the plantaris tendon rather than fascia lata in the second stage for attachment to the coronoid process.

In many of the operative descriptions throughout the book, one is constantly alerted to numerous other sections of the book by page and figure number causing much confusion, loss of continuity of description and time in jumping around for information and/or illustrations.

The chapter on cleft lip and cleft palate repair describes the most successful techniques and eliminates the older techniques, which in this day and age would be unacceptable.

Undoubtedly, the newest and most intriguing concepts that have been developed in Plastic Surgery in recent years are the contributions of Doctor Paul Tessier of Paris to the treatment of hypertelorism and craniofacial dysostosis, which opens vast new area for correction of these defects, previously considered beyond the reach of reparative surgery, but other than a note to refer to this work, descriptions and discussions are absent and I feel this field should have been touched upon in such a fine text.

In breast surgery for repair of gynecomastia, one should be wary of resecting the breast tissue through an incision half of the circumference of the areola, as described, particularly in a large male breast, for shrinkage and a deep central depression of the nipple often will occur.

All of us in the field are familiar with the various repairs of bilateral abnormal protrusion of the ears with absence of the antihelix and those experienced in the field, know that cutting the cartilage, folding it and holding it in place with a Lembert-type suture for formation of the antihelix results in a sharp and undesirable edge. Therefore, its description in the text would perhaps best be eliminated.

The chapter on blood vessels is not really too informative and lacks present day concepts on the newer methods of repair. The classical hemangiomas and lymphangiomas are not discussed or illustrated and they certainly play a formidable part in our practice.

The description in the several chapters on repair of tendons, nerves, and vessels particularly of the hand are quite complete, particularly good are the illustrations and descriptions borrowed from Bunnel's text and illustrations in color done by Frank Netter, M. D. Functional restorations and cinoplasty are well illustrated, whereas the congenital malformations of the hand are only briefly discussed and

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Reconstructive Surgery of the hand in Leprosy is not mentioned.

For sake of completion, it would have been well to retain the sections on repairs of the foot as he did in previous editions of his book. If the book, of necessity, had to be shrunken, it would have been well to eliminate all of the orthopedic problems, some of which are quite voluminously described and which, I believe, belong in the specialty of orthopedic surgery.

In my mind, the heart of this book lies, not so much in the description of the repairs, but in Doctor May's personal background and familiarity with the German language, enabling him to integrate his previous European experiences to his American experiences. Where he preferred one procedure to another, he has made it relatively plain and experiences in surgical procedures are thus emphasized. One cannot but be particularly impressed by the extensive bibliography at the end of each chapter, not only of older publications, but also of the most recent relevant literature. The book, although voluminous and authoritative, is enjoyable reading for one already familiar with the field and serves as a reference source for each of the areas covered. For the embryo Plastic Surgeon, it may be somewhat more complicated in scope, but it could well serve as a review of the field for them, rather than a practical working manual. The clinical photographs and drawings are of high quality and one can only respect his accomplishments. The convenience of having this vast storehouse of information in one volume makes it a valuable addition to a surgeon's library and I do recommend it as a reference work for all surgeons interested in the field of Plastic and Reconstructive Surgery.

ALFRED J. SURACI, M.D.

Medicine and Ethnology. ERWIN H. ACKERKNECHT. H. H. Walser and H. M. Koelbing, Editors. Price, $10.00. Pp. 195. Baltimore: The Johns Hopkins Press, 1971.

Dr. Ackerknecht's selected essays offer a point of view about the differences between primitive and scientific medicine which anyone interested in the history of medicine should carefully consider, since it is based on properly selected and thoughtfully analyzed ethnological data. Basically, Dr. Ackerknecht looks at primitive medicine as an important part of a total cultural pattern in various particular groups, rather than as a crude precursor of modern scientific medicine. That is, medicine in various primitive cultures has three basic functional (and primarily non-biological) aspects: 1) a *magical aspect* (always predominant over any rational aspect); 2) a *social aspect* (whereby "sickness" and "treatment" are heavily imbued with social sanctions); and 3) a *psychopathological aspect.* In regard to the latter, Ruth Benedict showed that not everything is psychopathological in a primitive culture that appears so to an outsider, although mental disease in primitives (recognized as such by both natives and outsiders) does exist and often manifests itself in so-called states of involuntary possession. For example, in a very interesting and well-documented essay entitled, "The Shaman and Primitive Psychopathology in General," Ackerknecht describes the ways medicine men in various cultures are subject to trancelike "states of possession," which are voluntary, often induced by drugs, and are differentiated from possession-disease states despite apparent similarities. In certain special cases, psychopathology plays an important role in the life of the medicine man. For example, the Siberian shaman is an individual who passes through a stage of very marked mental disturbance, analogous to an acute schizophrenic reaction. However, he is more or less cured of his affliction if and only if he accepts the call to become a shaman.

Ackerknecht's essays, originally published in the early 1940's in various journals of anthropology and medical history, contain fascinating illustrations from anthropological literature to back up his general points. His description of the differing roles of medicine in the cultures of Cheyennes, Dobuans, and Thongas is particularly absorbing, and it adequately supports his conclusion, "there is not one primitive medicine, but there are numerous primitive medicines," since there are widely varying supernatural conceptions of the nature of disease, all reflecting social conflicts and ideology more than events in nature. With the advent of scientific medicine and its progressively more and more successful control of the natural phenomena of disease, medicine has lost most of its "sacred" character and its social control function, becoming more of a function of society and less of a regulator of it.

NORMAN L. WILSON, M.D.

medical annals of the district of columbia

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Management and Treatment of Tropical Diseases. B. G. MAEGRAITH AND H. M. GILLES, Editors, Price, $26.50. Pp. 786. Oxford and Edinburgh: Blackwell Scientific Publications, 1971.

This handbook is a compilation of succinct articles on a variety of tropical illnesses, mixed helter-skelter with chapters on a variety of well-known non-tropical illnesses. It is intended for the express use of physicians in the tropics (not to be left out we are told are the physicians who practice in other areas of the Third World, wherever that is), who need a fast source of not terribly in-depth information about illnesses especially prevalent in under-developed areas of the world. The contributing writers, 44 in all, and mostly African or Asian, lend to their discussions the particular flavor of their unique experience, i.e. their daily contact with parasitic illnesses, and the special demands that the care of any illness in warm under-developed countries seem to impose on the physician.

The discussions of the many non-tropical illnesses are distinguished only for their eminent readability. Several of the discussions are very brief, and serve only to acknowledge that certain diseases exist, for example, a paragraph which discusses anuria in children informs us that this condition is "fortunately rare" and requires special management. So much for that little problem. Physicians have access to better books in or out of the tropics.

As a textbook of tropical diseases (the ones caused by parasites and other organisms) it is worthwhile. There are some moments that bring you up short, however. The bibliography that follows a synoptic chapter on eosinophilic lung cites the author's original article as the sole reference. We learn, particularly for those interested in one-upmanship in soul-cooking, how to prepare Mpotompota, a yam and fish concoction, as well as Kontomire stew, each calculated to provide concentrated protein supplementation ("when preparing stew for a young baby do not add pepper").

The recurrent emphasis on the art of the care of tropical peoples who become ill, diminishes the need for this book by any of us, although there are generous discussions of the treatment and prevention of tropical maladies, including some surely never heard of in medical school. We are indebted to our medical colleagues in these primitive areas of the world for giving us an overview of the medical care over there where life can be short and the art long.

GEORGE A. TRALKA, M.D.

An ABC of Medical Genetics. C. O. CARTER, F.R.C.P. Price, $4.50. Pp. 94. Boston: Little, Brown and Company, 1969.

This fine little volume was reprinted from seven articles in The Lancet, to which the author added two more chapters. It is a concise and lucid presentation of the fundamentals of genetics together with their application in medical practice. The author does not suggest that the reader will be an expert in medical genetics or in genetic counselling. The careful reader will find much information of value, as well as an awareness of how omnipresent medical genetics is becoming in medicine.

The final chapter, on "Prospects in the Control of Genetically Determined Disease," discusses in an excellent manner the preventive medicine techniques available today, as well as future applications as new techniques become available. The author firmly believes that the individual, or the couple, should be informed of the hereditary risks. Once these are known, the individuals should make their own decisions. The author indicates that a risk for an affected infant of one in ten or less is acceptable for most people, especially if techniques for analyzing amniotic cellular material and amniotic fluid are accessible.

STEELE F. STEWART, JR., M.D.

Wolff's Headache and Other Head Pain. Revised by DONALD J. DALESSIO. Price, $19.50. Pp. 688 with illustrations. New York: Oxford University Press, 1972.

This book is a compendium on headache and headache related syndromes. It was first published in 1948 and represents the third edition of this valuable work. The basic formula remains essentially unchanged. The book discusses all of the classical headache patterns and deals both with their mechanisms and with their treatment. There is an excellent bibliography attached to this book with over a thousand references.

This work is suitable for both the specialist and the generalist in helping them both better understand and deal with the various manifestations of headache problems.

The book begins with a general consideration of pain and pain-related structures, and a classification of headache patterns. This is followed by distinct descriptive material of the various headache syndromes and their treatment. To those familiar with this book in the past, some new chapters on cranial arteritis and analgesic abuse have been added. On the other hand, some of the existing chapters have been updated and in some instances trimmed.

I personally found the book most informative, particularly in some of the more obscure relationships of headaches to focal and systemic disorders. The information is concise, the explanations are clear, and the therapeutic suggestions most helpful. At the end of every chapter is a summarization of the most salient features that have been discussed. There are frequent anecdotes illustrating particular types of headache problems. For example, there are interesting descriptions of headaches associated with diabetes mellitus; migraine and the relationship to birth control pills; and headaches associated with disorders of the temporal mandibular joint.

Considering the book as whole, it is an excellent reference on headaches and any of its varied manifestations. In view of a changing therapeutic approach to cephalgia, a brief treatment supplement could be useful at yearly intervals.

MARVIN C. KORENGOLD, M.D.

Current Therapy—1972. HOWARD F. CONN, M.D., Editor. Price, $16.50. Pp. 836. Philadelphia: W.B. Saunders Company, 1972.

This volume in its 24th edition, like Hoagy Carmichael's Stardust, has become an American evergreen.

The contents are divided into 17 sections which include the several body systems and a number of broad disease categories such as infections, metabolic and allergic disorders. Within these sections the management of each of the principle medical problems is discussed by one or more experts. These discussions generally provide a brief description of the disorder, followed by the general and specific measures employed by the contributors. Both generic and trade names are used.

Some idea of the scope of the book may be obtained from the number of contributors, nearly 350, and the number of disorders discussed, almost 300.

Current Therapy is in no sense a textbook of medicine. Its greatest value will be to the physician who has a clear grasp of pathophysiology, and who wishes to review his options when confronted with the problems of day to day practice.

One might offer the criticism that this book is sometimes too arbitrary. Yet is this characteristic which makes it so useful as a daily companion to the busy practitioner. I personally find its presence on my shelf a comfort.

JAMES E. FITZGERALD, M.D.

Early Care of the Injured Patient. COMMITTEE ON TRAUMA, AMERICAN COLLEGE OF SURGEONS. Price, $9.00. Pp. 441 with illustrations. Philadelphia: W. B. Saunders, 1972.

The book, edited by Drs. Curtis Artz, Thomas Ballantine and Oscar Hampton, but written by the entire Committee on Trauma of the American College of Surgeons, presents in its twenty-four chapters an excellent, quick reference review on care of the injured. It emphasizes the acute phase of treatment. The material is presented in a very organized fashion with excellent indexing, making quick referral a very easy task.

The text, although ideal for medical students and interns, would do well in the library of any emergency room or doctor's office where acute injuries are seen. For the fully trained surgeon it presents a quick, easy and accurate review of trauma in general. The initial chapters on Cardiopulmonary Resuscitation, Shock, Infection and Anesthesia are particularly good. The chapters on bone injuries are detailed, excellently organized and ideal for the untrained when faced with skeletal injuries.

In summary, "Early Care of the Injured Patient" is an easy to read, concise and quick to the point text, which would be an asset to anyone's library, particularly if caring for injured patients.

CARLOS A. SILVA, M.D. F.A.C.S.

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Practical Management of the Elderly, 2nd edition. W. FERGUSON ANDERSON. Price, $12.50. Pp. 382. Oxford and Edinburgh: Blackwell Scientific Publications, 1971.

The medical profession realizes that there is a rapidly growing population of old people throughout the world. To come to grips with the basics involved in managing them is the main thesis of the above publication.

The introduction in chapter one presents a descriptive explanation of the background needed to understand the subsequent chapters. The author begins by stating, "old people who are ill are unwell not because they are old but because there is some disease process present. Normal attributes change with age, so that iatrogenic disease must not be produced by trying to modify an age-adjusted attribute to that of a young person." An attempt is made to differentiate categories of old people and their required needs of accommodation to sharing and living in their environment.

Some 29 chapters cover many phases pertaining to the aged and aging, i.e.: graphic presentation of norms in normal and abnormal aging in various parts of the world; work and retirement; problems in diagnosis. Separate chapters are devoted to specific systemic diseases in the old, as well as community organizations and services available to them. The author discusses the disease preventive approach and its problems of diagnosis.

The chapters on physical health, mental health and accidents at home concerning the aged should be underscored. Such subjects as diseases of the gastrointestinal tract, heart, respiration, blood, endocrine system, genitourinary system, strokes and common neurological diseases, mental disorders, locomotor system, disturbances of electrolytes and water, selection of elderly patients for surgery, accidental hypothermia, nutrition for the elderly, diseases of the eyes and skin, and care of the dying are fully discussed. The author does not go into these specific clinical entities in depth. Medical textbooks would make better references in this regard.

The chapter on accidental hypothermia and nutrition of the elderly were significantly analyzed and worth reading.

There are suggestions at the end of the book dealing with the practical approach in handling such problems as methods of treatment of aging for the medical student, postgraduate teaching of the general practitioner, preparation of old workers for retirement and listing of mechanical equipment useful for helping old people in ambulation and general usefulness.

The author emphasizes understanding the relationship existing between older people, their families, nurses, medical practitioners and social agencies. Understanding teamwork is necessary for the efficient management of the elderly. The author discusses specific problems of old age and exhibits a well planned organization and grasp of his material, so that a better understanding in correlating all factors is reached.

The material in the book is comprehensive enough and written in non-dogmatic manner, well organized and unusual. The manuscript is an informative approach to a better and useful understanding of the factors involved in the handling of the aging and the aged.

This book should be in every medical libarary dealing with Geriatrics. I recommend it as required reading for nurses, social workers and community social agencies personnel who have to deal with management of the aged.

ALLAN E. LEE, M.D., F.A.C.C.

Laboratory Tests in Diagnosis and Investigation of Endocrine Function, 2nd edition. ROBERTO F. ESCAMILLA, Editor. Price, $23.50. Pp. 456. Philadelphia: F. A. Davis Company, 1971.

The subject matter for this book was taken from a post-graduate course presented at the University of California Medical Center in California. The publication date of the book is 1971 but we are not told the date at which the original course was held, although one would guess from the references the material which is covered that it was probably presented sometime in late 1969 or 1970. This is a multiple authored book and covers the following topics: Pituitary, Thyroid, Parathyroid, Pancreatic Islets, Adrenals, Testis, and Ovaries. The authors included some distinguished clinicians and investigators, almost all of them from the University of California in San Francisco. There are some excellent sections and some which fall down in their content and literary style. Much of the problem with Escamilla's book is the fact that may of the tests discussed and their applications have changed markedly in the past two years. For example, there is no mention in the pituitary section of serum radioimmunoassays for gonadotrophins which are now the investigative tool of choice in assessing the intactness of these hormones. In other ways, the authors at times lack discrimination listing every test which could ever be done in evaluating the pituitary but failing to tell the interested reader which tests are most valuable and why. In the chapter on "Clinical Diagnosis of Pituitary Disease" for instance, Dr. Escamilla writes of using BMR cholesterol and serum carotene to assess TSH function but such tests in general are non-specific and of little value. The serum TSH done by radioimmunoassay which has been developed lately, is much more useful and to the point.

Some of the standout chapters in the book included a valuable discussion on the thyroid by Greenspan with an excellent table of the thyroid tests which would be value to every clinician. In addition, Dr. Hibbard Williams has written an excellent chapter on "Unusual Carbohydrate Metabolic Disease" as has Grumbach on "Pathogenesis and Diagnosis of Abnormalities of Sexual Differentiation" and "Sex Chromatin, Chromosomes and Sexual Anomalies."

"Laboratory Tests in Diagnosis And Investigation Of Endocrine Function," does not always speak of laboratory tests and often does not help the clinician in knowing what tests to do, how to do them or when. The aim of Dr. Escamilla's book is worthy one and with the help of such excellent writers as Drs. Biglieri, Williams, Greenspan, Gordon, Fortune, Nelson and Odell, one would have expected a superb treatise. Unfortunately, some of the other authors fall short of the goal, and in its entirety the book cannot be recommended for general usage. However, the chapters cited above are excellent ones for review for the endocrinologist. For the general internist and medical student, the book has little to recommend it. Other works serve a better purpose and other review articles have dealt with the same subjects in better detail.

W. TABB MOORE, M.D.

Vectorcardiography in Congenital Heart Disease. R. CURTIS ELLISON, M.D. AND NORMA J. RESTIEAUX, M.B., CH.B. Price, $13.50. Pp. 209 with illustrations. Philadelphia: W. B. Saunders Company, 1972.

Vectorcardiography is now an established tool in the diagnostic armamentarium of heart disease. This book limits itself to the specific area of congenital heart disease encountered in the pediatric age group. The first four chapters enable the beginner to grasp and understand the basic principles of vectorcardiography. It is lucid, presented in a simple manner, and achieves its objective.

The succeeding fourteen chapters are devoted to the vectorcardiographic features of specific congenital cardiac lesions. It also represents the experience derived from the several thousand cases seen in one institution. As one might expect, the vectorcardiogram had its greatest predictive value in the assessment of ventricular hypertrophy. The table of normal values from birth to early adult as well as the sequential VCG changes in the various congenital cardiac malformations will serve as a valuable reference for all who use vectorcardiography in the pediatric age group. The book will have limited appeal to the practicing clinician.

ANTONIO C. DELEON, JR., M.D.

An ABC of Endocrinology. K. J. CATT, M.D. Price, $5.95. Pp. 154. Boston: Little, Brown & Company, 1972.

"Brevity is the soul of wit." Thusly, one may characterize the presentation of knowledge in "An ABC of Endocrinology" by K. J. Catt. An avalanche of information is presented succinctly in straightforward terms; complete and to the point. The information rendered is current and enumerates a thorough description of the subjects covered.

Each glandular system and its by-products are described with the chemistry and physiology thereof; presented with rare clarity and completeness. I recommend this tiny volume to all interested in Endocrinology, in fact, to all who are interested in how to present a vast subject well in a few pages.

MAX G. SHERER, M.D.

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If continuing to operate as you are is best for you, we'll tell you so—and suggest a long-range financial program that's best for you in that situation.

And if you're *already* incorporated, we'll still be happy to review your present plan and your operations to make sure you're not missing any potential benefits.

All you have to do to get started is call Jack Pollock, Senior Trust Officer, at (202) 624-3002. We'll take care of the rest.

Because whether you're a doctor or a corporation, we're ready with everything you need today to make tomorrow better.

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BANK OF
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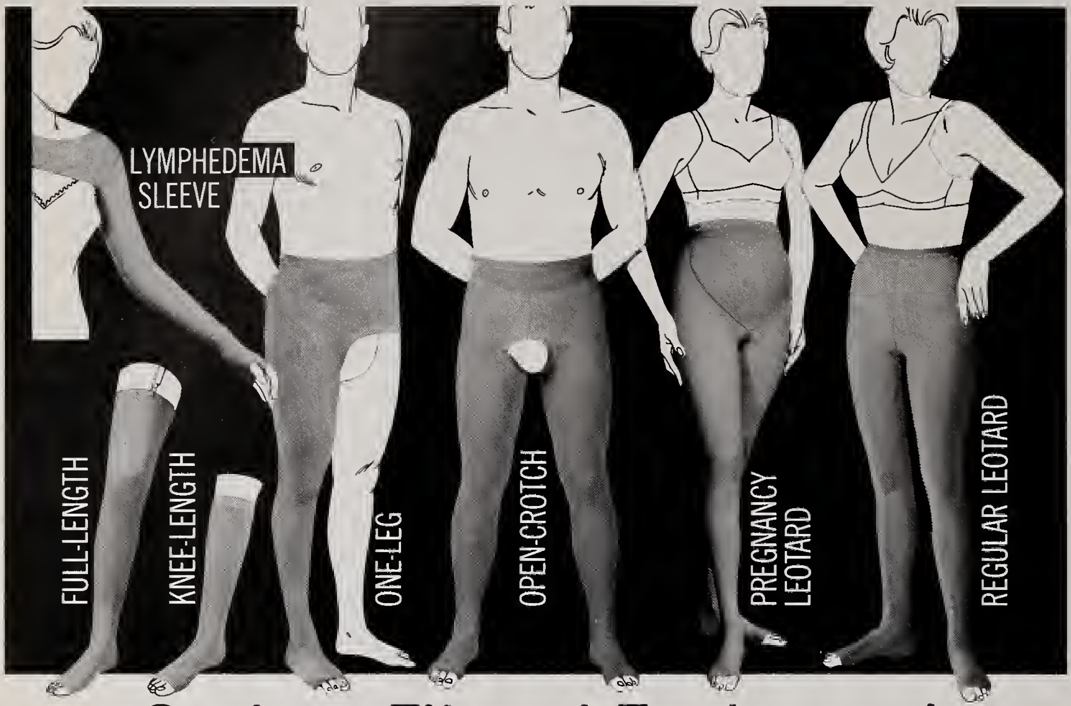
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Jobst Venous Pressure Gradient® supports are custom-made and precisely fitted to the contour of the affected extremity of the individual patient in a series of careful measurements.

Even more *important* than the perfect fit, are the exact counterpressures built-in according to your own prescription!

Jobst Venous Pressure Gradient® elastic stockings are a treatment of *choice* for leg ulcers, varicose veins, stasis dermatitis, postmastectomy lymphedema, post-phlebitis syndrome, post-fracture, post-operative and injury edema.

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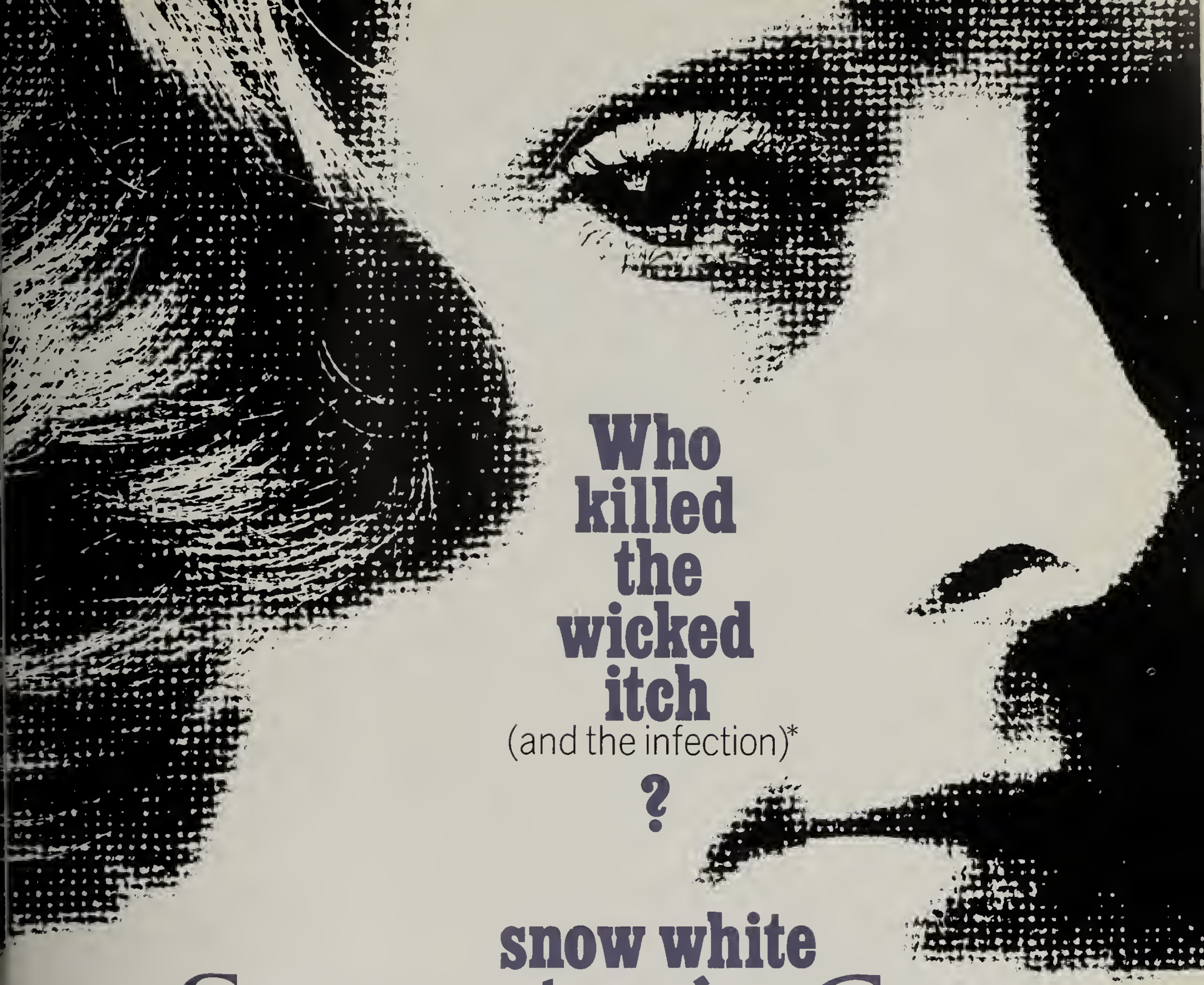


Who killed the wicked itch (and the infection)* ?

snow white

Sporostacin Cream

TRADEMARK

(chlordantoin 1% and benzalkonium chloride 0.05%)

Sporostacin Cream
Sporostacin Cream

After you write your prescription for two tubes of soothing, fungicidal Sporostacin Cream, tell your patient not to be fooled by the quick relief of symptoms it affords. Make sure she knows how to use it as directed—for the *full* 14-day course of therapy. Then, on follow-up, you'll usually find that nonstaining, easy-to-use Sporostacin Cream has finished off vulvovaginal candidiasis in the nicest possible way.

two tubes...two weeks

* **Indication:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: For the treatment of vulvovaginal candidiasis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: None known. **Precautions:** Cases of sensitization and irritation have been reported. When noted the drug should be discontinued. **Dosage:** One applicatorful intravaginally twice daily for a period of 14 days. Course of therapy may be repeated if necessary.

Ortho Pharmaceutical Corporation · Raritan, New Jersey 08869 Ortho © OPC 1972

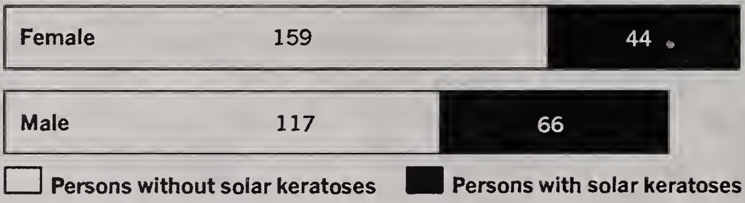
What it means to live and work in Tipton County, Tennessee

Persons who are white and over 40 have one chance in four of having solar keratoses... which may be premalignant

An epidemiologic study* conducted in Tipton County, Tennessee, revealed that 28.5% of white persons over 40 had solar keratoses; most had multiple lesions. Cluster sampling projected an estimated prevalence of 32.5% for white males and 19.5% for white females.

Though this is an unusually high percentage of affected persons, these lesions can occur in any white population, wherever people work or play out of doors.

Prevalence of solar keratoses in white persons over 40 in Tipton County, Tennessee



*Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey.

Solar, actinic, senile keratoses

Called by many names, the typical lesion is flat or slightly elevated, brownish or reddish in color, papular, dry, adherent, rough, sharply defined; usually multiple lesions, chiefly on exposed portions of the skin.

Sequence/selectivity of response

Erythema in areas of lesions may begin after several days of therapy; height of reaction (only in affected areas)* usually occurs within two weeks, declining after discontinuation of therapy. Since this response is so predictable, lesions that do not respond should be biopsied to rule out the presence of a frank neoplasm.

Cosmetic results

Cosmetic results are highly favorable. Incidence of scarring is low—important with multiple facial lesions. Efudex should be applied with care near the eyes, nose and mouth.

5% cream-a Roche exclusive

Only Roche formulates the 5% cream... high in patient acceptability... high in clinical efficacy, especially for lesions of hands and forearms... economical.

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Multiple actinic or solar keratoses.
Contraindications: Patients with known hypersensitivity to any of its components.
Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.
Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.
Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.
Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.
How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.
Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

an alternative to conventional therapy

Efudex®
(fluorouracil)
cream/solution

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One cancer you can give yourself.
Horrible isn't it?
AMERICAN CANCER SOCIETY

PRESCRIBING INFORMATION

Antiminth (pyrantel pamoate) Oral Suspension

Actions. Antiminth (pyrantel pamoate) has demonstrated anthelmintic activity against *Enterobius vermicularis* (pinworm) and *Ascaris lumbricoides* (roundworm). The anthelmintic action is probably due to the neuromuscular blocking property of the drug.

Antiminth is partially absorbed after an oral dose. Plasma levels of unchanged drug are low. Peak levels (0.05-0.13μg/ml.) are reached in 1-3 hours. Quantities greater than 50% of administered drug are excreted in feces as the unchanged form, whereas only 7% or less of the dose is found in urine as the unchanged form of the drug and its metabolites.

Indications. For the treatment of ascariasis (roundworm infection) and enterobiasis (pinworm infection).

Warnings. *Usage in Pregnancy:* Reproduction studies have been performed in animals and there was no evidence of propensity for harm to the fetus. The relevance to the human is not known.

There is no experience in pregnant women who have received this drug.

Precautions. Minor transient elevations of SGOT have occurred in a small percentage of patients. Therefore, this drug should be used with caution in patients with pre-existing liver dysfunction.

Adverse Reactions. The most frequently encountered adverse reactions are related to the gastrointestinal system.

Gastrointestinal and hepatic reactions: anorexia, nausea, vomiting, gastralgia, abdominal cramps, diarrhea and tenesmus, transient elevation of SGOT.

CNS reactions: headache, dizziness, drowsiness, and insomnia. Skin reactions: rashes.

Dosage and Administration. *Children and Adults:* Antiminth Oral Suspension (50 mg. of pyrantel base/ml.) should be administered in a single dose of 11 mg. of pyrantel base per kg. of body weight (or 5 mg./lb.); maximum total dose 1 gram. This corresponds to a simplified dosage regimen of 1 cc. of Antiminth per 10 lb. of body weight. (One teaspoonful = 5 cc.)

Antiminth (pyrantel pamoate) Oral Suspension may be administered without regard to ingestion of food or time of day; and purging is not necessary prior to, during, or after therapy. It may be taken with milk or fruit juices. Because of limited data on repeated doses, no recommendations can be made.

How Supplied. Antiminth is available as a pleasant tasting caramel-flavored suspension which contains the equivalent of 50 mg. pyrantel base per ml., supplied in 60 cc. bottles.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Clean sweep

PINWORMS 0
ROUNDWORMS 0
STAINS 0
ARTHUR

with a single dose of Antiminth (pyrantel pamoate) ORAL SUSPENSION

Highly effective against pinworm and roundworm

Non-staining to teeth or oral mucosa on ingestion, to stools, clothing, linen

Simple dosage with a single-dose regimen: 1 cc. per 10-lb. body weight (1 tsp./50 lb.; maximum dose, 4 tsp.)

Well-tolerated, based on clinical studies*

Pleasant-tasting, easy-to-take, caramel-flavored oral suspension

Economical, because one prescription can treat the entire family

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

ANTIMINTH®
(pyrantel pamoate)

equivalent to 50 mg. pyrantel/ml.

ORAL SUSPENSION

While Antiminth is highly effective against pinworms and roundworms, the illustration is not meant to imply 100% efficacy.

*Data on file at Roerig.

Please see prescribing information on facing page.

IN ASTHMA
IN EMPHYSEMA

optional therapy

THE mudranes®

All Mudranes are bronchodilator-mucolytic in action, and are indicated for symptomatic relief of bronchial asthma, emphysema, bronchiectasis and chronic bronchitis. **MUDRANE tablets** contain 195 mg. potassium iodide; 130 mg. aminophylline; 21 mg. phenobarbital (Warning: may be habit-forming); 16 mg. ephedrine HCl. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline-phenobarbital-ephedrine combinations. **Iodide side-effects:** May cause nausea. Very long use may cause goiter. Discontinue if symptoms of iodism develop. **Iodide contraindications:** Tuberculosis; pregnancy (to protect the fetus against possible depression of thyroid activity). **MUDRANE-2 tablets** contain 195 mg. potassium iodide; 130 mg. aminophylline. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline. **Iodide side-effects and contra-indications are listed above. MUDRANE GG tablets** contain 100 mg. glyceryl guaiacolate; 130 mg. aminophylline; 21 mg. phenobarbital (Warning: may be habit-forming); 16 mg. ephedrine HCl. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline-phenobarbital-ephedrine combinations. **MUDRANE GG-2 tablets** contain 100 mg. glyceryl guaiacolate; 130 mg. aminophylline. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions:** Those for aminophylline. **MUDRANE GG Elixir.** Each teaspoonful (5 cc) contains 26 mg. glyceryl guaiacolate; 20 mg. theophylline; 5.4 mg. phenobarbital (Warning: may be habit-forming); 4 mg. ephedrine HCl. **Dosage:** Children, 1 cc for each 10 lbs. of body weight; one teaspoonful (5 cc) for a 50 lb. child. Dose may be repeated 3 or 4 times a day. Adult, one tablespoonful, 4 times daily. All doses should be followed with ½ to full glass of water. **Precautions:** See those listed above for Mudrane GG tablets.

MUDRANE—original formula
First choice

MUDRANE-2
When ephedrine is too exciting or is contraindicated

MUDRANE GG
During pregnancy or when K.I. is contraindicated or not tolerated

MUDRANE GG-2
A counterpart for Mudrane-2

MUDRANE GG ELIXIR
For pediatric use or where liquids are preferred

Clinical specimens available to physicians.

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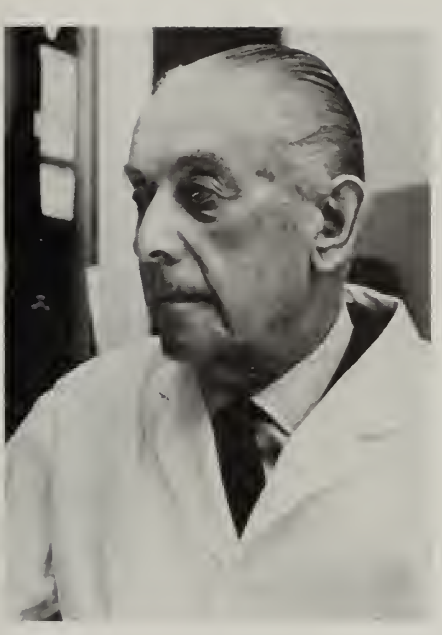
Manufacturers of Ethical Pharmaceuticals

obituaries



Willy E. Baensch, M.D.
1893–1972

Dr. Willy E. Baensch, an internationally known radiologist, died November 1, 1972. He resided at 5911 Onondaga Road, Bethesda, Maryland.

Born in Magdeburg, Germany, he studied medicine at the universities of Munich, Leipzig and Halle. He received his M.D. degree from the University of Halle. While studying physics at Munich, he was an assistant to Wilhelm Conrad Roentgen, discoverer of roentgen rays and winner of the Nobel Peace Prize in physics in 1901.

After four years of clinical training at Halle, Dr. Baensch specialized in radiology. He was an assistant to Professor Forsell at the Radiumhemmed in Stockholm, Sweden, and then became assistant to Madame Curie at the Curie Institute in Paris. He completed his training under Professor Holzknecht in Vienna.

In 1927 the University of Leipzig appointed Dr. Baensch to build a modern institution of radiology. He later became its director and a professor of radiology there.

During that time he wrote over 100 articles on X-ray diagnosis and treatment of cancer with X-ray and beta radiation. With Professor Hans Rudolf Schinz of the University of Zurich Dr. Baensch wrote Roentgendiagnosis, a four-volume text published in six editions and five languages.

Dr. Baensch was elected president of the Roentgen Congress in Europe in 1934 and secretary general of the International Congress of Radiology in 1937.

He came to the United States in 1946 and was invited to join the Georgetown University medical faculty as professor of radiology and chairman of the Department of Radiology, positions which he held until 1967. At the time of his death he was professor emeritus and consultant to the Georgetown Department of Radiology.

Dr. Baensch received the Golden Medal from the Georgetown University Hospital, the Riedermedalle from the German Roentgen Society and was elected an honorary member of the German Roentgen Society. He was also a consultant to the Veterans Administration Hospital, the National Institutes of Health, the American Medical Association and D. C. General Hospital.

Dr. Baensch was a Life member of the Medical Society of the District of Columbia.

He is survived by his wife, Hilda L., of the home address; two sons, Christian E. of Washington, D.C. and Robert E. of New York; and three daughters, Tina E. Raver of New York, Mrs. Wied de Brujn of Holland and Mrs. John MacNeil of Alexandria, Virginia.

John Kachmarick, M.D.
1938–1972

Dr. John Kachmarick, a Washington area psychiatrist, died November 11, 1972. He resided at 6053 Tammy Drive, Alexandria, Virginia.

Born in Philadelphia, Pennsylvania, he received his undergraduate education at Villanova University and his M.D. degree from George Washington University School of Medicine here. He served his internship at Scranton State General Hospital and his residency at Saint Elizabeths Hospital. He had been a Medical Officer in Psychiatry at Saint Elizabeths Hospital since August 1968.

Dr. Kachmarick was an Active member of the Medical Society of the District of Columbia.

He is survived by his wife, Roberta, of the home address.

Frank S. Horvath, M.D.
1892–1972

Dr. Frank S. Horvath, former professor of medicine and medical director of the Outpatient Department of the Georgetown University School of Medicine, died November 9, 1972 in Fort Lauderdale, Florida.

Born in Cleveland, Ohio, he received his undergraduate education in Hungary and his M.D. degree from the Royal Hungarian University of Budapest. He served his internship at the Municipal Hospital of Budapest and his residence at the Liget and Park Sanitarium in Budapest. His other postgraduate training included a fellowship in radiology at the University of Budapest and work in Internal Medicine and Cardiology at the St. Elizabeth Sanitarium in Balatonfured, Hungary. He practiced medicine in Hungary for a time before returning to the United States in 1931.

Dr. Horvath joined the Georgetown University medical faculty in 1939. He was a clinical professor of medicine there at the time of his retirement in 1969. He had been on the staffs at Georgetown University, Doctors and Children's Hospitals, and at the Washington Hospital Center.

Dr. Horvath was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, and a past President of the Washington Heart Association.

A Life member of the Medical Society of the District of Columbia, he also held membership in the American Medical Association, the Southern Medical Association, the Atlantic Dermatologic Association and the American Academy of Dermatology.

He is survived by his wife, Yolanda, of Coral Springs, Florida, and three sons, Peter N. and Alexander B., both of Bethesda, Maryland, and Laurence B., of Miami.

Emile C. Nash, M.D.
1919–1972

Dr. Emile C. Nash, chief medical officer of the Howard University Medical Service at D.C. General Hospital, died November 22, 1972. He resided at 4307 18th Street, N.E.

Born in Canton, Mississippi, he received a B.A. degree from Tougaloo College in Mississippi and his M.D. degree from Meharry Medical College in Nashville, Tennessee. He served his internship and residency at Hubbard Hospital in Nashville. He was also a Rockefeller Foundation Fellow at the University of Chicago.

Dr. Nash was an assistant and then associate professor of medicine at Meharry Medical College, and instructor at the University of Pittsburgh College of Medicine and a ward physician at the Veterans Administration Hospital in Pittsburgh.

He joined the faculty at the Howard University College of Medicine as an associate professor in 1959 and became a professor of medicine in 1969. He had been with the university's medical center at D.C. General for 13 years.

An Active member of the Medical Society of the District of Columbia, Dr. Nash was also a member of the Medico-Chirurgical Society and the D.C. Chapter of the American Federation of Clinical Research. He was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine.

He is survived by his wife, Eva W., and two daughters, Michele L. and Sharon E., of the home address; a brother, Leon, of Detroit, and two sisters, Mildren South and Vertile Maultsby, of Chicago.

Clayton Hawfield, M.D.
1901–1972

Dr. Clayton Hawfield, who practiced general medicine in the Washington area for more than 40 years, died November 6, 1972. He resided at 1625 Upshur Street, N.W.

Born in Monroe, North Carolina, he received his undergraduate education at the University of North Carolina, where he was an outstanding tackle on the football team. He received his M.D. degree from George Washington University School of Medicine here. He served his intership at the old Emergency Hospital here and his residency at Episcopal Hospital in Philadelphia. He established his practice here in 1930, from which he retired in October, 1971.

A life member of the Medical Society of the District of Columbia, Dr. Hawfield was also a member of the American Medical Association and the American Academy of General Practice.

medical annals of the district of columbia

vol. 42 no. 2 february 1973

He is survived by his wife, Mary F., of the home address; two daughters, Helen Stephens, of Pittsburgh and Norine Sprague, of Rochester, New York; a sister, Amelia Price, of Monroe, North Carolina; two brothers, R. Roy and Frank, also of Monroe, and two grandchildren.

Solomon Katzenelbogen, M.D.
1890–1972

Dr. Solomon Katzenelbogen, a retired psychiatrist, died November 3, 1972. He resided at 9305 Parkhill Terrace, Bethesda, Maryland.

Born in Ouman, Russia, he received his medical degree from the University of Geneva, Switzerland, in 1918. In 1919 he was an assistant in pathological anatomy and otolaryngology at the University of Zurich.

A member of the internal medicine faculty at the University of Geneva from 1920 to 1925, he became head of that staff in 1925.

In 1928 Dr. Katzenelbogen joined the staff of Johns Hopkins School of Medicine as an associate professor of psychiatry, where he remained until 1938.

From 1938 to 1953 Dr. Katzenelbogen was director of laboratories and research at Saint Elizabeths Hospital here, and served as clinical professor of psychiatry at the George Washington University School of Medicine from 1939 to 1959. He also maintained a private practice from 1959 until his retirement in 1971.

He did extensive work on the barrier between blood and cerebrospinal fluid, the effect of sleep on the blood, hypertension, and psychotherapy.

An Associate member of the Medical Society of the District of Columbia, Dr. Katzenelbogen was a fellow of the American Psychiatric Association and the American Neurologic Association.

He is survived by his wife, Nina G., of the home address, a daughter, Eva Sober of Bethesda, and two grandchildren.

Thomas A. Egan, M.D.
1902–1972

Dr. Thomas A. Egan, a retired Washington ophthalmologist, died October 21, 1972 while vacationing at South Lake Tahoe, California. He resided at 2500 Fordham Road, Alexandria, Virginia.

Born in Jersey City, New Jersey, he was a graduate of Fordham University and received his M.D. degree from Georgetown University School of Medicine here. He served his internship at Mary Immaculate Hospital in Jamaica, New York, and his residency at the old Episcopal Eye, Ear and Throat Hospital here.

He had been on the staffs of the Episcopal, Georgetown University, Children's, Doctors and the old Gallinger hospitals, and was a staff member emeritus of the Washington Hospital Center. He had also been a consultant to the District of Columbia and Alexandria, Virginia health departments.

In 1946 Dr. Egan was a member of a team of doctors and dentists sent by the Department of the Interior to Attu and Kiska to make a study of Eskimos.

He had been a clinical associate professor of ophthalmology at Georgetown University School of Medicine and had taught there for more than 25 years.

An Active member of the Medical Society of the District of Columbia, he was also a member of the Georgetown Clinical Society.

Dr. Egan is survived by his wife, Margaret Oertly Egan, of the home address; a son, Thomas A., Jr., of Sacramento, California, and two grandchildren.

*desirable associates

*office space

*ancillary services

*may be obtained thru . . .

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in the MEDICAL ANNALS

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The Rx that says "Relax"

BUTISOL Sodium provides highly predictable sedative effect: minor dosage adjustments are usually all that's needed to produce the desired degree of sedation. (With 3 dosage forms and 4 strengths to make adjustments easy.)

BUTISOL Sodium offers prompt, smooth, relatively non-cumulative action: begins to work within 30 minutes. . . yet, because of its intermediate rate of metabolism, generally has neither a "roller-coaster" nor a "hangover" effect.

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These are four good reasons for prescribing BUTISOL Sodium for the many patients who need to have the pace set just a little slower. Its gentle daytime sedative action is often all that's needed to help the usually well-adjusted patient cope with temporary stress.

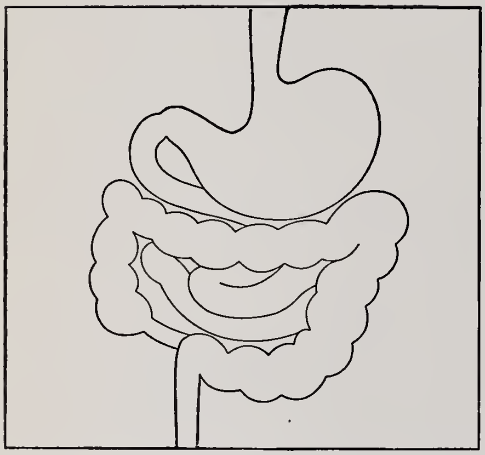
*Based on surveys of average daily prescription costs.

Butisol SODIUM®
(SODIUM BUTABARBITAL)

Contraindications: Porphyria, sensitivity to barbiturates, or susceptibility to dependence on sedative-hypnotics. **Warning:** May be habit forming. **Precautions:** Exercise caution in: moderate to severe hepatic disease; withdrawal in drug dependence or the taking of excessive doses over a long period, to avoid withdrawal symptoms; elderly or debilitated patients, to avoid possible marked excitement or depression; use with alcohol or other CNS depressants, because of combined effects. **Adverse Reactions:** Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and gastrointestinal disturbances are seldom seen. **Usual Adult Dosage:** For daytime sedation, 15 mg. to 30 mg. t.i.d. or q.i.d. For hypnosis, 50 mg. to 100 mg. **Available as:** Tablets, 15 mg., 30 mg., 50 mg., 100 mg.; Elixir, 30 mg. per 5 cc. (alcohol 7%). BUTICAPS® [Capsules BUTISOL SODIUM (sodium butabarbital)] 15 mg., 30 mg., 50 mg., 100 mg.

McNEIL McNeil Laboratories, Inc., Fort Washington, Pa. 19034

in
“Gasspastic”
conditions



The GI tract in spasm is commonly a “gas trap.”

Sidonna® is formulated to release entrapped gas, as well as to provide antispasmodic/sedative effects.

In addition to the traditional combination of belladonna alkaloids and butabarbital (warning: may be habit forming.), Sidonna contains simethicone—a non-systemic defoaming agent that “lyses” gas bubbles on contact.

Sidonna has the ability to relieve GI spasm, pain **and gas** in the irritable bowel syndrome, spastic colon, pylorospasm, gastroenteritis, gastritis, nausea, nervous indigestion, or gastric and duodenal ulcer.

Sidonna can calm GI spasm...control anxiety...and release entrapped GI gas from the system.

Sidonna can do more for your “gasspastic” patient. Try him on 1 or 2 tablets before meals and at bedtime.

Sidonna®

Each scored tablet contains: Specially activated simethicone 25 mg.; hyoscyamine sulfate 0.1037 mg., atropine sulfate 0.0194 mg., hyoscine hydrobromide 0.0065 mg. (equivalent to belladonna alkaloids [as bases] 0.1049 mg.) and butabarbital sodium N.F. 16 mg. (Warning: May be habit forming.)

can do more

Contraindications: Anticholinergics should not be used in patients with glaucoma, known prostatic hypertrophy, or pyloric obstruction. Urinary retention may indicate the presence of prostatic hypertrophy. If it occurs, the dose should be reduced or the drug withdrawn. Also contraindicated in patients with known hypersensitivity to one of the components.
Side Effects: Dryness of the mouth, blurred vision, dysuria, skin rash, constipation or drowsiness may occur.

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PHYSICIAN WANTED: Ob-Gyn; Board eligible or certified, full- or part-time. Call Professional Recruiters, (301) 652-4540.

PHYSICIAN WANTED: Medical Officer for University Health Service, primarily serving 1,400 resident students. Requires D.C. license and staff privileges in a local hospital, preferably one located in the Northeast area. One-two hour office hours daily Monday through Friday during academic sessions; sharing "on-call" coverage other times. Submit resume and professional references to James E. Heffern, M.D., Medical Director, The Catholic University of America, Washington, D.C. 20017.

PHYSICIAN WANTED. A full-time physician is needed to administer routine medical care in a very modern 260-bed nursing home. Fringe benefits include hospitalization, life insurance and retirement program. Salary open, depending upon experience. Call Dr. L. J. Thomas, (301) 881-0300 for other details and interview.

OB-GYN: Board eligible or certified. A full- or part-time position is immediately available at PRETERM. Please call Dr. Jane Hodgson, (202) 298-6586.

MEDICAL OFFICER WANTED. Internal Medicine and other specialties will be considered. JCAH, 500 beds, 40 hour work week, no nights, evenings, Sundays or holidays. Government service, liberal fringe benefits. Unparalleled cultural, educational and recreational facilities in the nation's capital. Contact the Central Personnel Office, U.S. Soldiers' and Airmen's Home, Washington, D.C. 20315.

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- Dorsey Laboratories 7
- Geigy Pharmaceuticals 5
- Lederle Laboratories 4
- McNeil Laboratories, Inc. 11
- Ortho Pharmaceutical Corporation T-111
- Pharmaceutical Manufacturers Association 1–3
- William P. Poythress & Company T-116
- Reed & Carnrick 12
- A.H. Robins Company 93–95
- Roche Laboratories T-112–113
- J. B. Roerig & Company T-114–115
- G.D. Searle & Company T-68–70
- Smith, Kline & French Laboratories T-67
- Stuart Pharmaceuticals 6
  Division of ICI America Inc.
- The Upjohn Company T-89

Pharmacy
- Peoples Drug Stores T-88

Real Estate
- Presidential Towers (Twin Towers Associates) T-87
- Shannon & Luchs T-99

Sanitarium
- Kalorama Convalescent Home, Inc. 14

Services
- Communications Interconnect Corporation T-96

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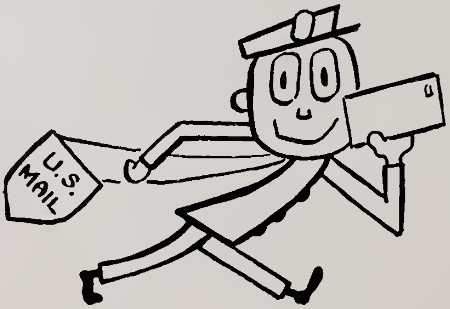

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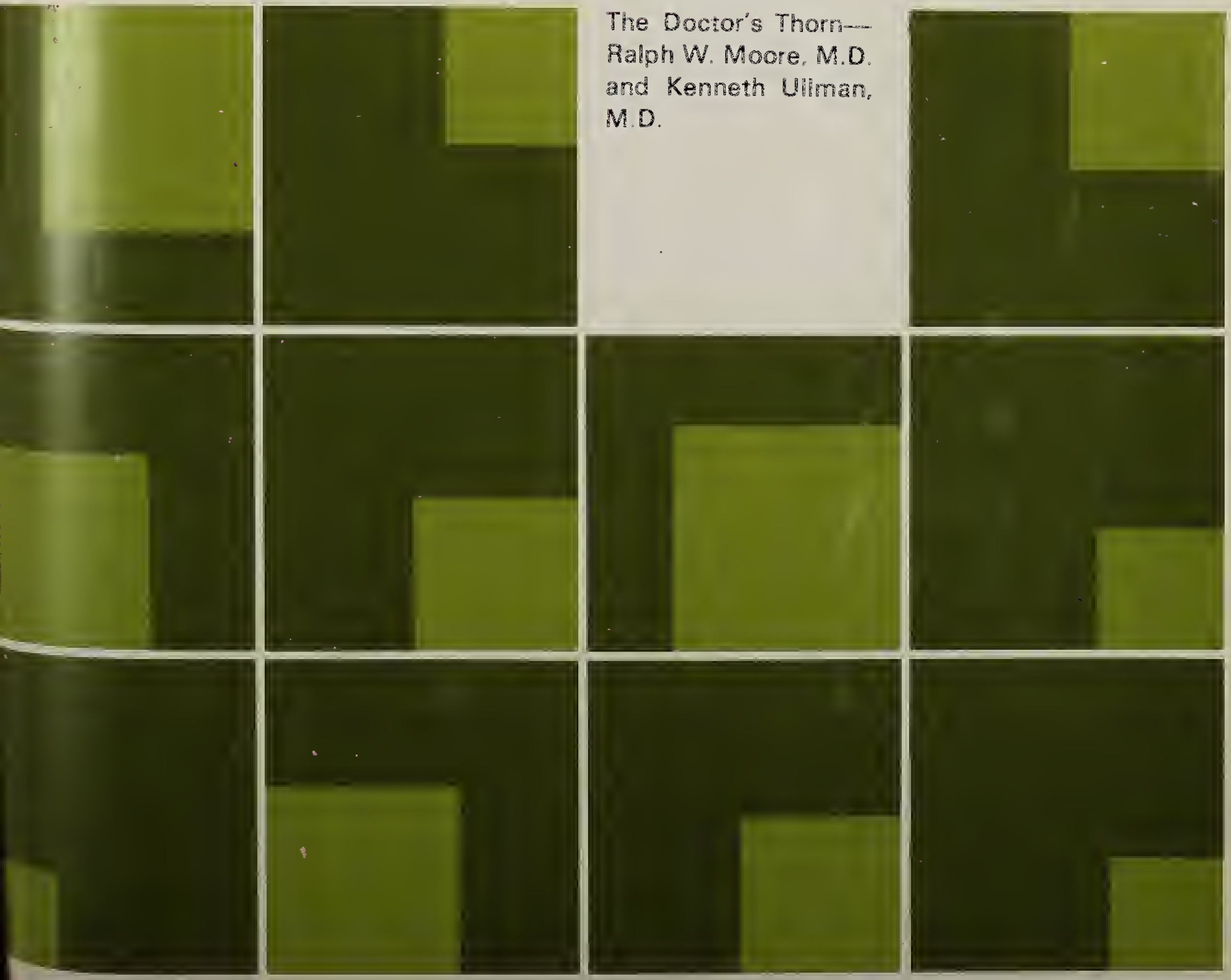

The Doctor's Thorn—
Ralph W. Moore, M.D.
and Kenneth Ullman, M.D.

volume 42 / number 3 / march, 1973

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SCIENTIFIC ARTICLES

The Doctor's Thorn. Ralph W. Moore, M.D. and Kenneth Ullman, M.D. 121

Management of Uncontrolled Thyroid Carcinoma. Domenic E. Sabatini, M.D. 124

Extraction of Catheter Fragment from the Pulmonary Bed by Non-Surgical Catheter Technique. James M. Bacos, M.D. and Michael R. Boivin, CVT 129

Treatment of Cardiogenic Shock. Lawrence S. Cohen, M.D. 132

Evaluation of Biologic Availability of Digoxin Preparations Available to a Naval Hospital. Walter V. R. Vieweg, CDR, MC, USN and Jonas Sode, CAPT, MC, USN 136

OTHER FEATURES

The View Box 145

Book Reviews 149

Hematology (Williams, Beutler, Erslev and Rundles) Reviewed by Harold S. Mirsky, M.D.

Current Pediatric Diagnosis and Treatment (Kempe, Silver and O'Brien) Reviewed by Andrew M. Margileth, M.D.

Air Pollution and Respiratory Disease (Holland) Reviewed by Alvin Seltzer, M.D.

The New Hospital Psychiatry (Abroms and Greenfield) Reviewed by Roger Peele, M.D.

A Consumer's Dictionary of Food Additives (Winter) Reviewed by Aaron G. Saidman, M.D.

Application of Proteolytic Enzymes to Protein Structure Studies (Mihalyi) Reviewed by A. Earl Vivino, M.D., Ph.D.

(continued)

Handbook of Medical Treatment (Chatton) Reviewed by Albert E. Marland, Jr., M.D.

Immunology, Immunopathology and Immunity (Sell) Reviewed by Daniel Ein, M.D.

Obituaries ... 161

Classified Advertisements ... 11

Index of Advertisers ... 13

Information for Authors ... 14

Advertising and Subscription Information ... 14

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"The Life So Short—the Craft So Long to Learn"

Hippocrates

Irving Burka, M.D.

Medical Records

There are many aspects of continuing education. It takes many forms. There are regular scheduled post-graduate courses in every speciality and subspecialty. There is the education obtained at regular scheduled ward round attendance; attendance at scientific sessions; medical conventions; subscription to various tape services; attendance at special lectures, and, of course, keeping up with the medical literature.

However, one facet of continuing education is very rarely consciously considered. That is the Medical Record. Such a chart, may be defined, as a *complete* account of the ongoing and continuing care of a patient as to diagnosis, therapy, complications, (if any), and disposition based on examination and ancillary procedures, (laboratory, etc.). Such an account is therefore often a mirror of the doctor's ability. It may reflect his knowledge, thought processes, ability, and conclusions. These may very well depend on his continuing education.

A peer review and utilization committee can quickly determine from such a record, when reviewed, the doctor's overall competence.

Recently, in a random review of several hundred medical records in doctor's offices a surprising finding was that some kept no records at all, and others kept such poor ones that it was almost impossible to arrive at any conclusions as to what was wrong with the patient, how he was treated, and whether the physician was competent. This is truly inexcusable!

As a profession, we always strived and will continue to strive for excellence. Let, therefore, our medical record keeping reflect this striving towards excellence, and be, indeed, a mirror of our competence.

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The Mounting Storm—Drugs

"The biggest drug dealer in your community may well be the good old family doctor and the pusher who supplies him is the pharmaceutical industry." Thus began the opening paragraph in a recent Washington Post article on drug abuse. Brutal? Undoubtedly. Overblown? Unquestionably. An element of truth? Just maybe. No matter how much or how little credence is given to such statements, it is illustrative of the fact that practicing physicians are being more frequently and volubly criticized for both sins of omission and commission in the area of drug abuse. That this may be a distortion of reality given substance by isolated, highly publicized medical infractions seems obvious to the practitioner—but not necessarily to his public—and so the storm shall continue to mount.

It does give one pause however—in considering our accomplishments in this most difficult area—to reflect on the recent day-long AMA-sponsored symposium on the medical complications of drug abuse. In featuring an unparallelled array of speakers before a standing-room only audience, only ten minutes were alloted for discussion of "treatment resources" . . . . ten minutes! In all fairness it must be emphasized that the conference orientation was indeed "medical complications," but it seems that any progress concerning cause, prevention, or treatment modalities was either "damned with faint praise" or worse, non-existent. One left the conference impressed by the armamentaria available to treat truly dire situations but feeling strangely impotent.

The emphasis seems, however, to be an accurate reflection of medicine as practiced daily. What physician has not treated the barbiturate overdose, the staphylococcal endocarditis, the serum hepatitis and—having weaned his patient through critical episodes—must discharge him back to the same environment at the same or greater risk to develop the identical illness in an identical manner. Impotence?

What then does this mean to the Washington area physician? To the individual perhaps little, in that sporadic, individual, outraged, voices accomplish little. The need is for concerted action, action in terms of:

1) Money—from private, local and federal sources to fund:

A) existing effective treatment programs at better than subsistence level, the level at which many are currently operating.

B) research for developing and evaluating innovative ways of coping with, if not solving the problem.

2) Public Relations:

A) to reorient by education a public more interested in the tactics of the offenders than the sources of their problem.

B) to disseminate to the public, as well as to physicians, drug guidelines as they are promulgated, such as the recent stand on amphetamine prescribing taken by the Medical Society of D.C. The patient requesting these drugs has as much a need to be aware of such guidelines as has the physician.

C) not least of all, to inform the public we are meeting the enemy and they are not us.

3) Pressure:

A) on the legislature for formulation of a sane, well-thought out policy on drug abuse, to replace ongoing crisis legislation.

B) on pharmaceutical houses and pharmacists, who must be as involved as we, to give their sorely needed support in an organized effective fashion.

C) on physicians, whose prescribing practices abet the abuse of drugs, to become aware that they must be part of the solution, not the problem.

It seems certain there will be changes, hopefully from within, but if not, sooner or later from Congress, prodded to action by the voices of an outraged constituency. Bringing about these changes will require an enormous expenditure of time, energy and money but we must begin with the single most necessary commodity—concern.

James G. Kane, Jr., M.D.

Electrocardiogram Comparisons

"When compared to the previous ECG, there is no (or there is) significant change." That is perhaps the most frequently made electrocardiographic diagnosis, but there is no published criteria that tells us how the electrocardiographer arrives at such a diagnostic statement. Nevertheless, the task of comparing ECGs is performed daily by thousands of readers all over the world. A few years ago we estimated the number of ECGs recorded in the United States to be about 50 million per year. This figure is probably much higher now. It is not infrequent to have a patient's hospitalization extended because changes (or lack of them) reported in serial ECGs "are not close enough to what the attending physician considers optimal."

In the past quarter of a century, and particularly in the last ten to 15 years, the advances in the field of electrocardiography have been numerous and impressive. A few ECG landmarks are: (1) the routine diagnostic clinical application of vectorcardiography, as proposed by Dr. R. P. Grant; (2) the use of digital computers in the automatic analysis and interpretation of the ECG; (3) the routine use of ECG monitoring in the operating and recovery rooms and the coronary care units; (4) the systematic use of the ECG in epidemiological studies; (5) the increasing use of the exercise ECG in the evaluation of the patient suspected of having coronary heart disease; (6) the recent understanding of the electrophysiology of cardiac muscle, cardiac arrythmias and conduction defects; and finally (7) improvements in ECG instrumentation and ECG transmission. The number of ECG papers published in recent years has increased several fold, culminating with the publication of the *Journal of Electrocardiology,* devoted entirely to the study of the ECG, but studies are lacking that demonstrate how well or how poorly we are currently applying these advances to the routine daily task of ECG interpretation, and particularly to the comparison of serial ECGs.

To dramatize for ourselves the current disastrous status of daily routine ECG comparison, one-hundred pairs (A and B) of serial ECGs were interpreted in the Heart Station by the attending cardiologist, assisted by two residents and one intern. Three categories were considered: (1) no change, (2) no significant change, and (3) significant change. The category of "significant change" had to be further identified or subclassified into a defined portion(s) of the ECG (P wave, PR segment, ST segment, T wave, etc.) and into a specific lead or leads. For the purpose of the study, the official Heart Station comparison statement was considered the "standard." These one-hundred pairs of ECGs (minus the

Heart Station statement) were then duplicated and sent to six cardiologists and four internists with interest and training in cardiopulmonary diseases. Their answers were compared with the "standard," and showed less than 50 per cent agreement with any aspect of the study. The detailed data of this study will be published in the near future.

These results, while disappointing, were anticipated. They emphasize that studies are urgently needed to precisely define when a given tracing can be said to be significantly different from the previous ECG and even more important, we must define at what level a change is significant for each of the different ECG parameters (waves, intervals, segments, etc.). Eventually these levels must be standardized. As we have demonstrated in previous published studies, data of this type can be only obtained by computing techniques, since human error and variation must be eliminated if ECG comparison is to be meaningful. Perhaps obtainment of this data will be the computer's greatest contribution to electrocardiography.

Finally, the comparison of accurately obtained levels between identical parameters in two serial ECGs must be correlated with clinical information, laboratory data, and whenever possible autopsy findings. This procedure is undoubtedly costly and time-consuming; on the other hand, we cannot afford to postpone this task any longer if ECG comparison is to have any scientific and objective value upon the documentation of the patient's progress (or lack of it). We must accept with humility that in the daily routine of ECG comparison we are indeed using a very small portion of what is currently known.

Juan B. Calatayud, M.D.

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> *"The history of science, and in particular the history of medicine . . . is . . . the history of man's reactions to the truth, the history of the gradual revelation of truth, the history of the gradual liberation of our minds from darkness and prejudice."*
>
> *—George Sarton, from "The History of Medicine Versus the History of Art"*

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Opinion

Results of a questionnaire to 7,000 physicians:

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Are there significant difference in bioavailability and clinica predictability among drug products

Teacher of Medicine

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I think that there can be a very great distinction between generic drugs and brand name drugs. And that applies to products of original research that have outlived their patent protection as well as to drugs that have long been in the public domain. Let me explain why.

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In terms of formulation, quality control, and the ability to reproduce an essentially identical product, batch after batch, I doubt that many firms are properly equipped to put out a product that is as carefully controlled as the product marketed by a pharmaceutical company with sophisticated research and high quality manufacturing facilities. For example, when a company comes out with its own preparation of a drug that has just lost its patent protection, there is no assurance that the drug it produces will be a therapeutic equivalent. The raw material could be identical and yet bioavailability might vary from complete unavailability to that which is equivalent to the original.

It Isn't Enough to Meet USP and NF Standards

Meeting USP and NF standards is not enough to guarantee therapeutic equivalence. In certain instances, stricter standards must be applied. Right now, the New York Heart Association has a committee that is studying the problem of digoxin equivalency. I am certain that they are going to recommend a bioavailability assay of a particular digoxin. Unless this is done, they will not recommend it for purchase or use in New York City hospitals. It represents too much of a hazard. They have gone so far as to recommend a batch-by-batch certification of bioavailability even though the company has been reproducing and marketing a digoxin product through the years.

The Problem of Controlling Bioavailability of Generics

The FDA does not have the manpower to inspect the quality control capabilities of hundreds of houses specializing in generic products. And I don't think that the average pharmacist is knowledgeable or aware of the quality and bioavailability of the infinite numbers of generic preparations. A recommendation has been made that every time a generic house (or for that matter a large pharmaceutical company) markets an already existing drug for the first time, a modified new drug application should be submitted. The manufacturer would have to show that his compound is the therapeutic equivalent of the standard compound in use, assuming that the standard compound is one that has been available for an extended period—say 15 years. This would be one indication that the control of bioavailability is beginning to get the attention that it deserves.

Clinical Predictability More Important Than Pr

Although the question
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xecutive Vice President
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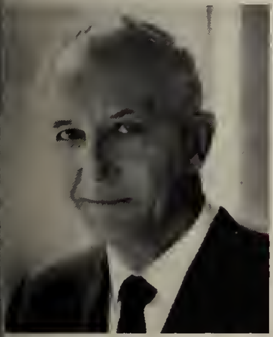

Although equivalence of ferent preparations of a *ug substance* may be de- ed by certain physical, emical or biological char- teristics, identity is not vays assured even though ese characteristics may described in compendia ch as the USP, NF or de- ned by other specific urce standards. More- er, even with equivalent ug substances, similar armaceutical *products* n be produced by differ- t manufacturers such at these products are bio- ically or therapeutically quivalent.

A Growing Awareness of Potential for Nonequivalence

As experience increases th drug substances de- ed from different sources d under different condi- ns, it should be possible establish specifications in ficient detail to minimize potential for their non- uivalence. However, ere is general agreement at product therapeutic uivalence would still not assured even if one could minimize nonequivalence of drug components produced by different manufacturers. Arguments relate largely to the extent of product inequivalences. Experience over the past six years has uncovered a greater incidence of nonequivalence of products prepared by different manufacturers from generically equivalent substances than many had previously surmised.

Newer Bioavailability Studies Reveal Differences

Bioavailability may be defined as a measure of the rate and amount of absorption of a drug substance from its administered dosage form. For several years pharmaceutical scientists have proposed that bioavailability data on presumably equivalent dosage forms provide the best measure of product equivalence—short of adequate clinical trial. In their continued search for shortcuts to the evaluation of product equivalence, medical and pharmaceutical scientists have increasingly relied upon bioavailability characteristics as reflected by blood levels of a drug after its administration to human subjects.

Leading manufacturers now conduct comparative bioavailability studies on their own product dosage forms after production process changes that would have been considered inconsequential a few years ago. This isn't surprising, since there are so many possible differences in production operations that the opportunities for inequivalent generic and brand name products are numerous—even when the production process begins with identical chemical substances. Moreover, reputable manufacturers are striving to improve *in vitro* control measures, such as dissolution characteristics, which are being related more meaningfully to bioavailability reference data.

As a result of advances in scientific instrumentation and analytical methodology which permit measurements of small quantities of drug substances in the body, our abilities to detect differences in bioavailability and possible therapeutic nonequivalance have appreciably improved.

Product Selection Based on Patient Response

Improved specifications and standards can better assure the equivalence of *drug substances*. Manufacturers, compendia and regulatory agencies can all play a part. However, it is the *drug product*, not the *drug substance*, that the physician, pharmacist, nurse and patient-customer utilize. How can these individuals make or influence specific product selections to minimize variations in therapeutic equivalence of multisource drugs? Patients' responses to a drug product provide a basis of experience to aid the physician in his selection of a particular product. The nurse and pharmacist can also help detect patient responses, but ultimate responsibility must remain with the physician.

Reputation of Manufacturer as Basis for Product Selection

The physician, to assure that his patients receive quality health care, must rely upon the capabilities of the reputable pharmaceutical manufacturer who is equipped to develop, prepare and control a quality product of uniform, reliable therapeutic performance. Substitution with purportedly equivalent generic products that are only superficially evaluated by an imitator manufacturer can place the health of the patient secondary to factors of price or convenience for the provider.

Opinion & Dialogue

**What is your opinion, doctor?
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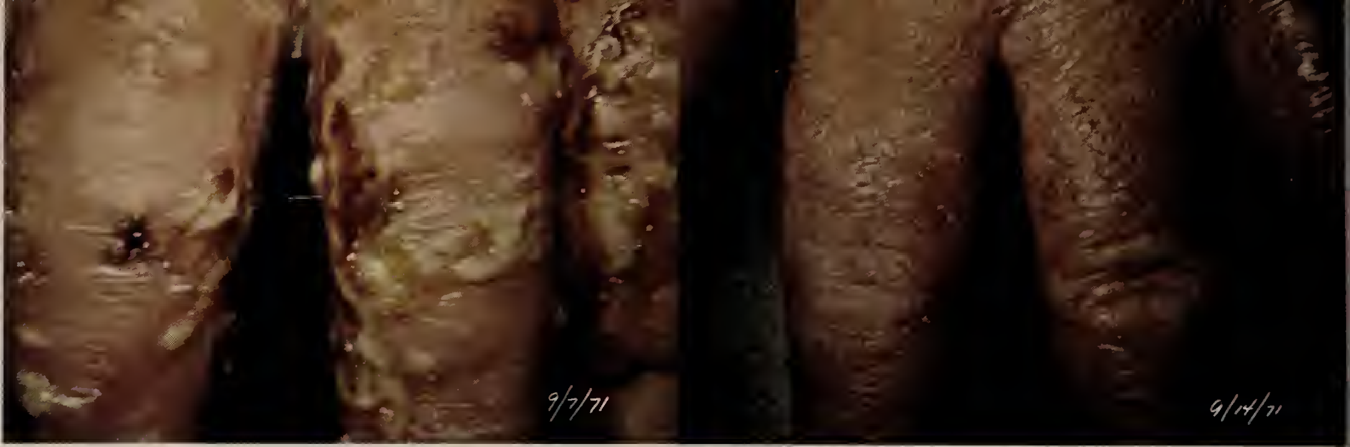

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Diagnosis: Severe pyoderma, left hand.
Culture: *Staphylococcus aureus, coagulase* positive and sensitive to MINOCIN.
Temperature: 102° F
Therapy: MINOCIN Minocycline HCl Capsules, 100 mg: 200 mg *stat,* 100 mg every 12 hours. Medication began 9/7/71. By fourth day, temperature was normal and pustular lesions considerably improved. Last dose taken 9/14/71.
Concomitant therapy: None.†

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Contraindications: Hypersensitivity to any tetracycline.

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Precautions: Use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, institute appropriate therapy. In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and blood serology repeated monthly for at least four months. Because tetracyclines have been shown to depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of such dosage. Test for organ system dysfunction (*e.g.,* renal, hepatic and hemopoietic) in long-term use. Treat all Group A beta hemolytic streptococcal infections for at least 10 days. Avoid giving tetracycline in conjunction with penicillin.

Adverse Reaction: GI: (with both oral and parenteral use): anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in anogenital region. *Skin:* maculopapular and erythematous rashes. Exfoliative dermatitis (uncommon). Photosensitivity is discussed above ("Warnings"). *Renal toxicity:* rise in BUN, dose-related (see "Warnings"). *Hypersensitivity reactions:* urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus. In young infants, bulging fontanels have been reported following full therapeutic dosage, disappearing rapidly when drug was discontinued. *Blood:* hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia. *CNS:* (see "Warnings.") When given in high doses, tetracyclines may produce brown-black microscopic discoloration of thyroid glands; no abnormalities of thyroid function studies are known to occur.

NOTE: Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption; do not give to patients taking oral minocycline. Studies to date indicate that absorption of MINOCIN is not notably influenced by foods and dairy products.

***Indicated in infections due to susceptible organisms. Culture and sensitivity testing recommended. Tetracyclines are not the drugs of choice in the treatment of any staphylococcal infection.**

†Case Report, Clinical Investigation Department, Lederle Laboratories.

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Indications: Acute gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existence of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
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The Doctor's Thorn

RALPH W. MOORE, M.D.* AND KENNETH ULLMAN, M.D.†

Abstract

The Munchausen Syndrome creates difficulties in diagnosis and management. Two cases are presented that demonstrate the special role of physicians whom these patients seek to frustrate by their self-destructive patterns.

Avenues for intervention include "briefing" house staff and patients' families to facilitate psychiatric referral.

A patient may appear with complex medical problems who is truculent and evasive with a past history of psychiatric hospitalizations, drug addictions or prison sentences. He may be someone whose behavior will include quarreling with the doctors and nurses and making up falsehoods concerning the illness. This patient is then either discharged or signs out angrily. This pattern was named "Munchausen Syndrome" by Asher[1] and dedicated to Baron von Munchausen who traveled widely telling stories that were dramatic but untrue.

Recognizing the pattern of chronic hospitalizations and a desultory life style Asher suggested that possible motives for this behavior might include the need for interest from others, a grudge against doctors or hospitals, a need for drugs, a need to escape from the police, or free room and board. He noted that these patients were capable of wasting enormous amounts of time and were a source of trouble to their doctors.

Although Bagan reports that these patients did not have a grievance against doctors or hospitals, he did report their effect on the staff stating, "Never in the history of medicine have so many been annoyed by so few."[2] The thorny quality of these patients is commented upon by others[3, 4]. Spiro[5] noted in 14 of the 15 cases where ward behavior was described that there was a description of truculence, evasiveness and hostile behavior by these patients. In 22 of the 38 cases which he reviewed psychiatric consultation was omitted. In none of these patients were symptoms of drug withdrawal reported. Spiro studied one Munchausen patient for 45 hours of psychotherapy and obtained a history of how this patient had experienced several hospitalizations in close sequence around age four and at age 10 had witnessed the failure of doctors to save his father's life. This patient boasted at social gatherings that he was a doctor. Spiro felt that his patient identified with a pain inflicting physician and while he knew that he was acting he could not stop it.

When the clinical picture suggests Munchausen syndrome, the differential diagnosis includes a search for psychosis, for Cramer[6] observed that in two of his four patients evidence of overt psychosis existed in his patient's primitive thinking. Bleuler[7] used the term *psydologia phastastica* to describe patients who invented and maintained stories for long periods. He warned that this could be a forerunner to paresis or dementia praecox.

Can anything be done about these patients? Past attempts have included electroshock therapy, leucotomy, and the suggestion of creating a rogues' gallery that would be sent to local hospitals[8]. Cramer attempted to formulate a treatment based on an understanding of the patient's behavior. His four patients working in allied medical fields all acted seductively, managed to provoke physicians into operating or into discharging them angrily and all showed typical hysterical traits. He suggested that the central factor was a relationship with physicians who had been important figures to them. Unconsciously these patients acted out love and anger with their physicians. His two female patients claimed to have had love affairs with their physicians.

During the same week at Georgetown Medical Center two patients with this puzzling syndrome were seen. *Case Number One:* A 38 year old woman presented to the Emergency Room with hematuria of five days duration saying that she had sickle cell hemoglobinopathy and that she was allergic to IVP dyes. After being admitted she gave a history of "fits" and one of these fits caused great commotion as various anticonvulsants were tried only to fail. She loudly complained that she was not receiving adequate attention. Because she was conscious, without incontinence or post ictal confusion and could be suggested out of these "fits" psychiatric consultation was requested.

Her symptoms disturbed her husband as they occurred usually when he was entertaining company. He would respond by giving her a back rub or taking her to their local doctor.

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Significant past history include the following (1) serious illness as a child; (2) severe depression while working as a nurses' aide following the death of her father, necessitating psychiatric treatment for one year; (3) fits beginning some six years later (1965).

Her direct sensorial exam was negative and there was no evidence of hallucinations or thought disorder. She was observed by the psychiatric consultant (RM) to speak in a vague, unconcerned way about her "fits" and bleeding and unconvincingly denied inducing her urethral bleeding. She purposefully spit out anticonvulsant medication only to request the nurse to assist her in taking the medicine. She reported instant relief of pain when placebos were given. Subsequently she was observed by nurses to be scratching her genital area with blood observed under her finger nails. Reports from other hospitals included several documented self-traumas to the meatus and urethra by her nails and fingers with several instances of her signing out against medical advice and refusing to see a psychiatric consultant.

Consultations included hematology, gynecology, urology, neurology, and psychiatry. Routine lab tests as well as IVP, cystoscopy, urine cultures, EEG, skull films, brain scan, lumbar puncture, blood and spinal fluid VDRL were all negative.

Her ability to create tension in the ward personnel was prodigious. After both she and her husband were informed of the need for psychiatric help, which she refused, she was discharged. Her husband was advised not to reinforce her patterns by taking her to the emergency rooms but to take her to a psychiatric clinic. In spite of our advice he continued taking her to emergency rooms whenever she requested, however our "briefed" house staff were able to refer her to the psychiatric clinic without displaying annoyance or irritation towards her. This seemed to have some effect in that briefly she stopped coming to the emergency room and instead requested psychiatric help. However, shortly thereafter she returned to her previous patterns of eliciting annoyance from the staff of another hospital.

Case Number 2: A 38 year old divorced former registered nurse was admitted for evaluation of chest pain and dyspnea. Psychiatric consultation was requested because of a suspected functional etiology.

Her long medical history dating back to 1960 included many surgical procedures: pulmonary arteriography, bronchoscopy, bronchograms, venograms, exploratory laparotomy, and venal caval ligation. On this admission her medical evaluation included the following disciplines: medicine, surgery, gynecology, cardiology, pulmonary, and psychiatry.

The resident who was involved with her evaluation during a past hospitalization reported that she placed mascara on her lips to appear cyanotic, faked seizures, and pricked her finger to simulate hematuria. In this hospitalization, nurses reported that the patient had paroxysms of coughing when they entered her room but at no other time, and complained of pain which disappeared when engaged in conversation.

After becoming wildly agitated with dramatic crying at the idea of a psychiatric consultation, she procrastinated for several days and following a long talk with a priest she agreed to allow one of the authors (KU) to see her. Significant past history included that she was the oldest of four children, and that at age six she saw a psychiatrist because of a blinking problem. She described her mother as a perfectionist, and her father as an interested but distant figure, and talked in idealistic terms of her pediatrician who had a significant influence on her subsequent choice of nursing as a profession. At the time of admission and during at least one other hospitalization she dated a member of the hospital house staff. Her effect on her family included their bearing the expenses of the hospitalizations; on one occasion her parents were $20,000 in debt. Her mother's calling her daily from another city while she was hospitalized also reflects their involvement in her illness.

Despite her lying in bed with IV fluids, she appeared as a young looking attractive woman. She was cooperative, pleasant, and apologetically expressed her ambivalence over seeing a psychiatrist. She displayed no abnormal motor movements but she seemed mildly fidgety. She was very coquettish. Her thoughts revolved around her great boredom and disgust over her incapacitated position and she described herself as a sensitive, over emotional, and moody person. She denied delusions, hallucinations, illusions or phobias. There was no evidence of loose associations or perseveration in her stream of thought; her affect revealed indifference to "her long suffering" but some anxiety was evident at being interviewed. Her sensorial exam revealed the following: both recent and remote memory were intact, she performed serial seven's to 65 and then stopped arbitrarily. She recalled six numbers forward and five backward. Proverbs and judgment were good and her estimated IQ was 100-110.

When the patient was told that the following weekend a complete battery of psychological tests would be administered, she became quite apprehensive and began hyperventilating which terminated with further reassurance. Over the weekend the patient signed out against medical advice; however, an MMPI and figure drawing were done before leaving. The MMPI revealed an impulsive, immature, help-

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less individual with identity problems who would be expected to manifest neurotic symptoms under stress. Subsequently, she has undergone an exploratory laparotomy while in another state.

Discussion

Attempts to deal with these difficult patients have uniformly met with defeat. The doctor becomes provoked to anger, communicates this to the patient and in general feels relieved when the patient signs out AMA.

Many underlying dynamics have been postulated by Cramer. He relates the choice of a medical field for the stage of acting out conflicts to the fact that these patients have had significant relationships with physicians as adults and as children. The hospital setting is ideal for their need to provoke physicians and to identify with their fantasy of the pain-inflicting physician. The two cases reported by us seem to support these dynamics.

It is our contention that to interrupt the vicious cycle of the emergency room appearance—admission—doctor provoked hostility—signing out AMA, two approaches need to be considered. Neither of these approaches is unique; however, they have not been sufficiently advocated in dealing with these patients.

First, an intervention at the family level should occur, with an attempt to reduce the enormous secondary gain and reinforcement that these patients derive from their behavior. In our first case an attempt was made to communicate to the husband the need to discontinue his reinforcement of his wife's behavior, and in our second case the patient signed out before this could be accomplished. The second approach necessitates "briefing" the house staff and other local emergency rooms by bulletin to reduce the patient's gratification from provoking doctors into anger. It is our belief that by depriving the patient of this masochistic gratification we can alter the behavior pattern of the Munchausen patient and facilitate psychiatric referral.

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Management of Uncontrolled Thyroid Carcinoma

DOMENIC E. SABATINI, M.D.*

Thyroid carcinoma, although representing only 1% of all malignancies, remains a very important entity in our medical practice.

Surgery as the first modality of treatment is almost unanimously accepted. It has been our experience over the years, however, that beyond that point much confusion exists in the mind of the clinician. If the disease is not completely eradicated by the surgical procedure, should the patient receive external irradiation, a therapeutic dose of radioactive iodine or large doses of dessicated thyroid? We have seen again and again patients with undifferentiated carcinoma of the thyroid gland receive postoperatively very large doses of dessicated thyroid and those with the so-called "pure" papillary carcinoma not receive treatment with radioactive Iodine I_{131} on the basis that this tumor would not concentrate the isotope. Why so much confusion?

The purpose of this paper is to present several cases which occurred in our practice, and try to reach from them some conclusions as to the best management of uncontrolled thyroid carcinoma.

Report of Cases

Case 1. N. H., a 23-year-old Negro was first seen in the Surgical Clinic in July 1969 with a two month history of enlargement of the neck. He was asymptomatic and denied hoarseness and dysphagia. The thyroid gland appeared diffusely enlarged, and a 3 cm hard nodule was palpable in the lower pole of the left lobe. Large lymph nodes were palpable in both cervical areas and one in the left supraclavicular area. A thyroid scan showed no evidence of function in the distal half of the left lobe. Chest X-ray films were negative. On August 13, 1969 two lymph nodes were excised from the right cervical area, and the pathological report was that of metastatic papillary carcinoma of the thyroid. On August 16, 1969 a total thyroidectomy and a modified bilateral radical neck dissection were performed. The primary tumor appeared located in the lower pole of the left lobe. There was extracapsular invasion involving the left side of the trachea and the left recurrent laryngeal nerve. At the time of surgery it was possible to preserve the left recurrent laryngeal nerve. The pathological report was that of papillary carcinoma involving both lobes of the thyroid with metastatic carcinoma in six lymph nodes in the left side of the neck and five in the right side. Following TSH stimulation, a scintiscan of the neck and chest was performed on September 11, 1969. It revealed concentration of radioactivity only in the mid-anterior cervical area just to the right of the midline. There was no abnormal concentration of radioactivity and no evidence of metastatic disease in the lungs or mediastinum. The patient was given 30 additional units of TSH, and on September 19, 1969 he received 100 mc of I_{131}. A scintiscan of the neck and chest 10 days later revealed large areas of increased radioactivity in the anterior cervical area extensive radioactivity in the lungs consistent with metastatic disease. (figs. 1, 2). The chest X-ray film was negative. He was also started on large doses of dessicated thyroid. Later scintiscans of the neck and chest and chest X-ray films have been negative. The patient

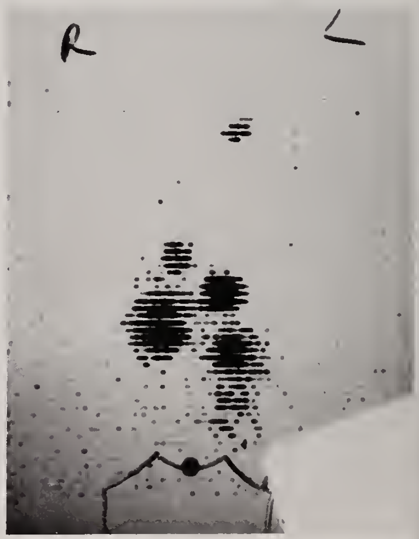

FIG. 1. Scintiscan of neck following total thyroidectomy for papillary carcinoma. Patient had received 10 days earlier 100 mc of I_{131}. Extensive disease is detected. A tracer dose had revealed only one small focus of disease.

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medical annals of the district of columbia

vol. 42 no. 3 march 1973

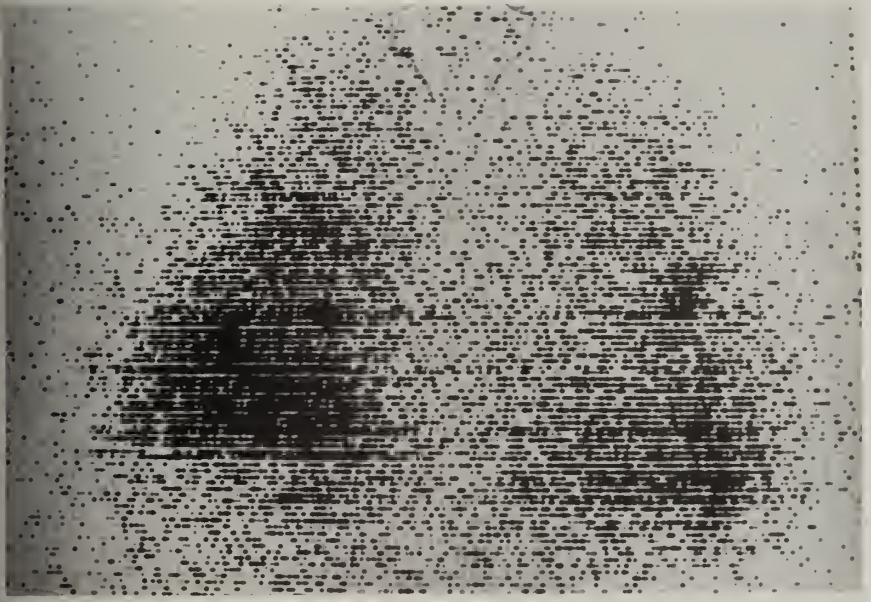

FIG. 2. Scintiscan of chest showing extensive metastases in lungs. A tracer dose had shown no evidence of disease.

has remained asymptomatic and free of disease.

Comment. It is our experience that patients with well-differentiated carcinomas with extensive disease grossly completely resected or with residual disease should be treated postoperatively with large doses of I_{131}. This treatment is indicated even if the scan following a tracer dose of I_{131} is negative. Small metastases which might not show up with a tracer dose will show up with a therapeutic dose of I_{131}.

Case 2. D. J., a 46-year-old Negro was admitted to the hospital on August 28, 1966 with a history of increasing hoarseness and mild dysphagia. The thyroid scan revealed the left lobe to be almost completely replaced by a 'cold' mass, and laryngoscopy showed paralysis of the left vocal cord. On August 29, 1966 a total thyroidectomy was performed. The large thyroid tumor was infiltrating the surrounding structures, being attached deeply to the thyroid cartilage and infiltrating the hypopharynx and upper esophagus. The left lobe was removed with extreme difficulty. The left recurrent laryngeal nerve was involved and it was sacrificed. Microscopic examination revealed follicular and papillary carcinoma. Foci of carcinoma were present in the right lobe and there was metastatic carcinoma in one adjacent lymph node. He was seen in consultation on September 27, 1966, at which time there was a large lymph node measuring 1.5 by 3 cm in the right submandibular area. The I_{131} uptake was 13%, and a scintiscan of the neck and chest revealed extensive radioactivity in the neck. The large lymph node in the right submandibular area revealed marked concentration of radioactivity (fig. 3). A therapeutic dose (100 mc) of I_{131} was given on September 27, 1966. Scintiscans of the neck, mediastinum and lungs in the following years failed to reveal any abnormal concentration of radioactivity. Since surgery the patient has been taking 5 Gr of dessicated thyroid daily.

Comment. These patients can live for many years a normal life, and repeated therapeutic doses of I_{131} and large doses of dessicated thyroid can control the disease for many years. The disease will also respond to external irradiation.

Case 3. A. P., a 23-year-old white woman, had a total thyroidectomy and bilateral neck dissection for a mixed follicular and papillary carcinoma on November 26, 1965. The tumor involved the right lobe and the isthmus, and there were metastases in the cervical lymph nodes and upper mediastinum. On December 21, 1965 metastatic lymph nodes were excised from the superior mediastinum in another hospital. The patient was first seen in consultation on April 22, 1966. She appeared in good general condition and completely asymptomatic. There were no palpable masses in the neck. Scintiscan of the neck and chest following a tracer dose of I_{131} and stimulation with TSH showed two large areas of increased radioactivity in the anterior cervical area. Widespread areas of increased radioactivity were also present in both lungs (fig. 4). The appearance was consistent with extensive metastases. The chest X-ray film was negative. The patient was given 100 mc of I_{131}. After determining the radioactivity present in the urine in the following days, it was estimated that the metastases had concentrated 17 mc of I_{131}. She was started on large doses of dessicated thyroid. A second scintiscan of the neck and chest on September 9, 1966 revealed only one area of increased radioactivity in the neck and none in the lungs or mediastinum. She received a second therapeutic dose of I_{131}. Since that time she has received large daily doses of thyroid hormone but has required no additional treatments with radioactive iodine. Subsequent scans have shown no evidence of metastases, and six years following the

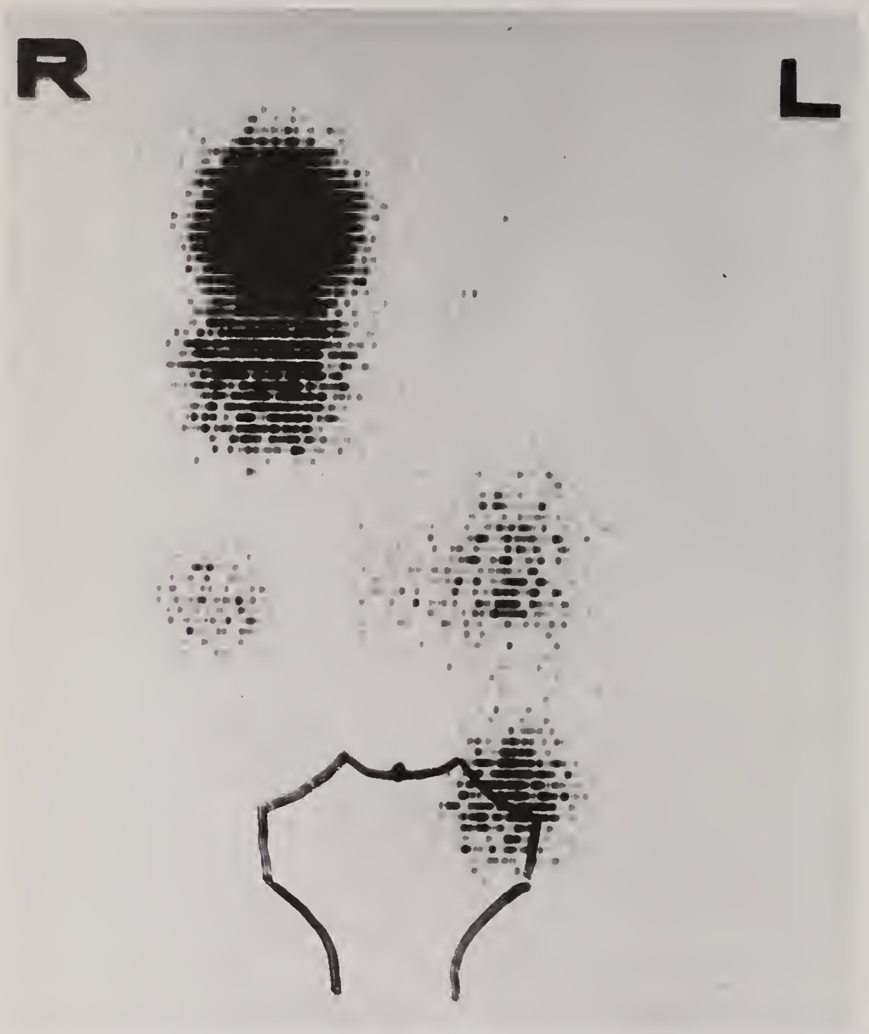

FIG. 3. Scintiscan of neck following total thyroidectomy for follicular and papillary carcinoma. Extensive residual disease is present.

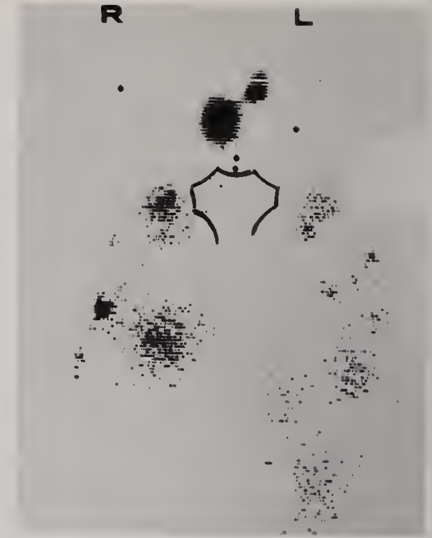

FIG. 4. Scintiscan of neck and chest following total thyroidectomy for a mixed follicular and papillary carcinoma. Extensive disease is present is neck and lungs.

first treatment with radioactive iodine she is free of disease.

Case 4. W. G., a 63-year-old white woman, had a nodule excised from the right lobe of the thyroid gland in July 1961. This was reported as benign. She later developed several thyroid nodules, and a total thyroidectomy and left radical neck dissection were performed in January 1963. The tumor was reported by some pathologists as Hurthle-cell carcinoma and by others as medullary carcinoma. During the next few years the patient developed recurrent soft tissue nodules in the right cervical area which were locally excised. In September 1965 a large, unresectable mass was found in the right supraclavicular area, and at that time deep X-ray therapy was given. The disease showed temporary involution, but in September 1967 two recurrent soft tissue nodules in the neck were found. The very large doses of thyroid hormone had not helped. In spite of the histology a therapeutic dose of radioactive iodine was contemplated in view of the ineffectiveness of any other therapy. Following stimulation with TSH the patient was given 100 mc of I_{131} on January 19, 1968. This treatment was not effective, the nodules continued to increase in size, and the patient died in a few months.

Comment. This was an undifferentiated carcinoma. Therapeutic doses of radioactive iodine and large doses of dessicated thyroid had no effect on the disease.

Case 5. R. K., a 59-year-old white man, had been treated 30 years earlier with Lugol's solution for hyperthyroidism. When first seen by me he had an asymptomatic goiter. He was admitted to the hospital on July 12, 1970 because of gradual enlargement of the thyroid gland, particularly the right lobe, associated with recent neck pain, hoarseness, slight dysphagia, and weight loss. Examination revealed a diffusely enlarged, firm thyroid gland, approximately three times normal size. There was a two cm lymph node near the upper pole of the right lobe but no other definite lymphadenopathy. Indirect laryngoscopy showed normal mobility of the vocal cords. On July 17, 1970 the neck was explored surgically. There was a diffusely enlarged, hard thyroid gland infiltrating into the pre-thyroid muscles and sternomastoid muscle on the right. It involved also the jugular vein, the carotid artery, and trachea, and there was fixation posteriorly on the right. The frozen section and the final pathological diagnosis was that of small-cell carcinoma. There was extensive inoperable disease. Only the isthmus and part of the right lobe of the thyroid gland could be removed. On July 22, 1970, following stimulation with TSH, the patient received 150 mc of I_{131}.

He was first seen in consultation in the Department of Radiation Therapy on September 2, 1970. He was completely aphonic and unable to swallow solid food. There was massive cervical lymphodenopathy in the right cervical area along the anterior and posterior triangles. This had appeared following the treatment with I_{131}. The thyroid gland was fixed to the adjacent structures. X-ray films revealed a large anterior superior mediastinal mass. There was marked narrowing of the hypopharynx and upper esophagus (fig. 5). From September 2, 1970 through October 9, 1970 he received deep X-ray therapy to both cervical supravicular areas and upper mediastinum for an ETD (estimated tumor dose) of 5,500 Rads (2 Mev-HVL 7.6 mm Pb). There was prompt and complete involution of the disease. An esophagogram and chest X-ray films then revealed no abnormality.

On January 1971 the patient developed urinary retention. A large fixed mass involving the left lobe of the prostate and extending to the left pelvic wall was found. A biopsy was reported as infiltrating anaplastic carcinoma consistent with metastatic small-cell carcinoma of the thyroid. The voice had markedly improved, and the dysphagia had disappeared. There had been complete involution of the cervical lymphadenopathy. A bone scan was compatible with metastases. Palliative irradiation to the pelvis and perineum was given, but the general condition gradually deteriorated, and death occurred one month later.

Comment. This patient had an advanced, inoperable, small-cell carcinoma of the thyroid gland. This is an undifferentiated carcinoma. Therapeutic doses of I_{131} and large doses of thyroid hormone were of no value. There was, however, an excellent symptomatic response to external irradiation. The demise was produced by distant metastases.

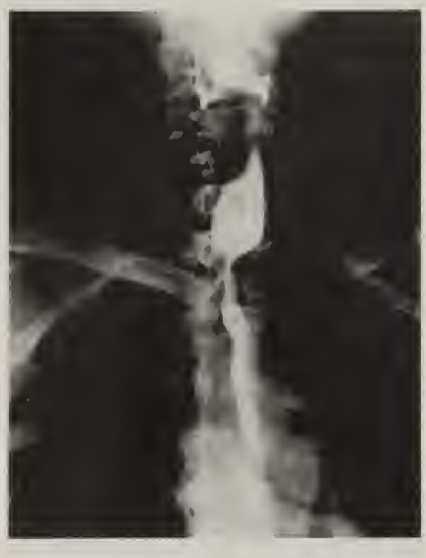

FIG. 5. Marked narrowing of hypopharynx and upper esophagus by an extensive, unresectable small-cell carcinoma of the thyroid.

Discussion

These five cases are not isolated but are examples of cases seen again and again in my practice. They suggest to me that, for treatment purposes, the thyroid carcinomas can be divided in two basic groups: well-differentiated and undifferentiated carcinomas. In my experience the well-differentiated carcinomas behaved as "functioning" carcinomas, whereas the undifferentiated carcinomas behaved as "non-functioning" carcinomas. "Functioning" carcinomas are hormonal-dependent, are stimulated by TSH, and pick up I_{131}. The "non-functioning" carcinomas are not hormonal-dependent, are not stimulated by TSH, and do not pick up I_{131}. As a result, large doses of dessicated thyroid and large doses of I_{131}, as well as external irradiation, could be used for an uncontrolled well differentiated thyroid carcinoma. Only external irradiation would be effective in the undifferentiated thyroid carcinoma.

The classification of G. H. Klinck et al[1] (table 1) seems excellent, not only on histopathological grounds but also as a guide to therapy. A simple glance at it would suggest to the clinician the best modality of treatment for an uncontrolled thyroid carcinoma. This classification appeals more than those suggested by Ibanez et al[2, 3] Wychulis et al.[4] by Woolner et al,[5] by Kheng Khoo Tan,[6] and by Hazard.[7]

The two main groups in table 1 appear to be a guide not only to therapy but also to prognosis. The well differentiated carcinomas have a much better prognosis than the undifferentiated ones.

In my experience the histology of the tumor was more important than the findings of the scan in determining therapy. Following a total thyroidectomy for papillary carcinoma, it is not infrequent to get a negative scan with a tracer dose of I_{131}, whereas a therapeutic dose of I_{131} will show marked concentration of radioactivity. Small metastases which might not show up with a tracer dose will show up with a therapeutic dose of I_{131}. Because of this I have treated all uncontrolled papillary carcinoma with

TABLE 1. Carcinoma of the Thyroid

Well differentiated:	1. Papillary 2. Follicular Mixed papillary and follicular Occult sclerosing papillary follicular
Undifferentiated:	1. Giant cell 2. Small cell 3. Medullary

large doses of I_{131} whether the scan was negative or positive. In all cases I have seen effective control of the disease. This experience does not seem to support the statements of Tubiana et al.[8] They base the therapeutic indication of I_{131} on the I_{131} uptake, scanning, and autoradiography of the specimen.

Summary

Our experience does not seem to confirm the statement often made that the extent of the disease and not the histologic type is most important to the prognosis.

Five cases of uncontrolled thyroid carcinoma have been reported. Three of them are well-differentiated carcinomas and two are undifferentiated carcinomas. The well-differentiated carcinomas responded well to large therapeutic doses of I_{131} and large doses of thyroid hormone. The undifferentiated carcinomas did not respond to therapeutic doses of I_{131} or large doses of thyroid hormone. The only effective therapy for them appeared to be external irradiation. This experience has been confirmed in many other cases.

If this experience is further confirmed, the terms "well differentiated" and "undifferentiated" could become synonymous with "functioning" and "non-functioning."

The functioning group is hormonal-dependent, is stimulated by TSH, and picks up I_{131}. The non-functioning group has opposite characteristics.

A classification of thyroid carcinoma has been recommended. It appears to give to the clinician a guide to therapy as well as to prognosis.

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Extraction of Catheter Fragment from the Pulmonary Bed by Non-Surgical Catheter Technique

JAMES M. BACOS, M.D.* AND MICHAEL R. BOIVIN, CVT†

Byline Washington Post: Baltimore—August 1972. "A 57-year-old patient successfully brought suit against a local hospital for additional hospitalization and the iatrogenic trauma of extensive chest surgery for the purpose of removing a three inch piece of intravenous tubing which had inadvertently sheared off and floated into the lung vessels. The patient contended that the fragment in his lungs was the result of neglect and that this and the subsequent surgery had caused him excessive physical and emotional pain and his well-being had been seriously jeopardized. The hospital settled for $115,000."

This news item is of singular importance since it points out a problem of increasing magnitude. Aside from the forensic aspects, there are even greater implications since catheter emboli left in situ invariably become infected and ultimately lead to death through continued sepsis and local erosion[1].

The following case report clearly demonstrates that catheter fragments in distal pulmonary vessels, may be successfully, easily, and simply removed with a minimum of equipment and without resorting to major chest surgery—all this to the emotional and economic relief of attending physicians and hospital administrators.

Report of Case

A 70-year-old female was admitted because of weight lose, diarrhea and hematuria of five months duration. Cystoscopy and biopsy revealed infiltrating carcinoma probably arising from the colon. After multiple post-operative complications, a CVP catheter was introduced for hyperalimentation. This catheter became dislodged and another one was introduced but approximately three hours later could not be flushed. At this time, a chest film revealed a six cm. fragment of tubing in the right mid lung field presumably having embolized from the subclavian vein out into the right pulmonary artery and into the lung bed (fig. 1a-b). Three days later, she became febrile. One week later, she was taken to the X-Ray Department where under fluoroscopic control, a

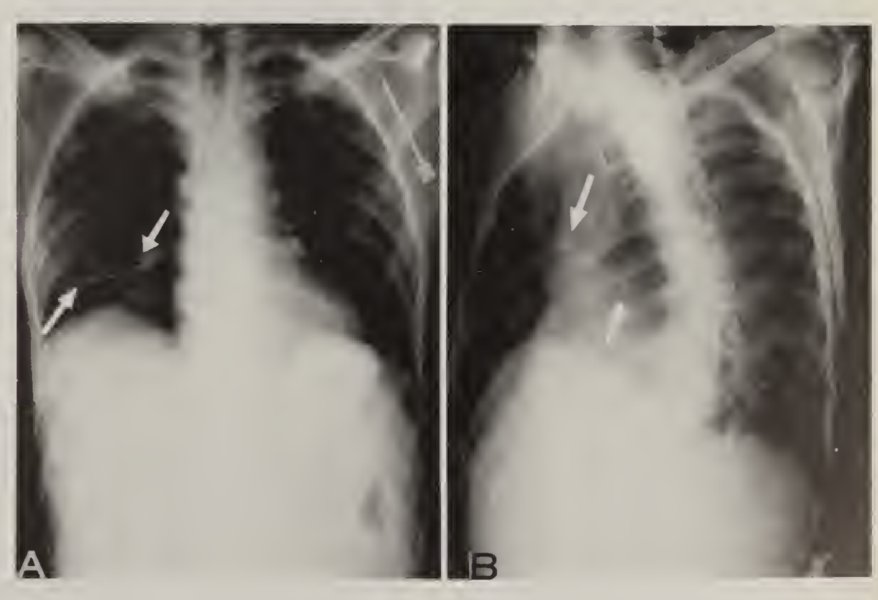

FIG. 1A. P-A of the chest showing catheter fragment in the right lower lung field. A "new" CVP Catheter is in the left subclavian vein. 1B. An oblique view of the fragment.

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cutdown was made over a branch of the left median basilic vein. Employing Massumi's loop-snare technique,[2] using a special wire* within a Cournand catheter, (fig. 2) the catheter, with the loop-snare withdrawn inside the tip, was passed with ease through the right heart and out into the right main pulmonary artery. With gentle manipulation, the tip of the catheter was then made to point in the direction of the right lower lung field where the catheter fragment was lying in a branch of the right pulmonary artery. At this point, the loop-snare was advanced beyond the tip of the catheter and as it did so it encircled the catheter fragment (fig. 3). Again, gentle manipulation of this snare caused movement of the fragment confirming its encirclement. The snare was then gradually pulled taut and as it did so, the fragment became secured to the tip of the cardiac catheter. The catheter, together with its attached polyethylene fragment, was then withdrawn into the main pulmonary artery (fig. 4) and then with one quick maneuver, pulled back to the region of the superior vena cava. It was then totally removed and placed in a sterile tray where a section of catheter fragment was removed and sent to the laboratory for bacteriologic testing (fig. 5). During this period, the patient experienced no symptoms whatsoever. The cutdown was then sutured and the patient sent to the ward in good condition.

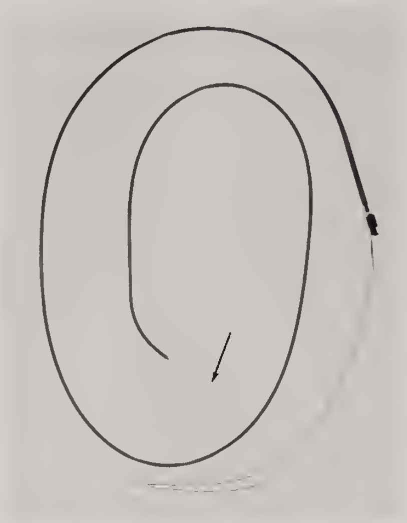

FIG. 2. Cournand Catheter with a wire within forming a loop snare.

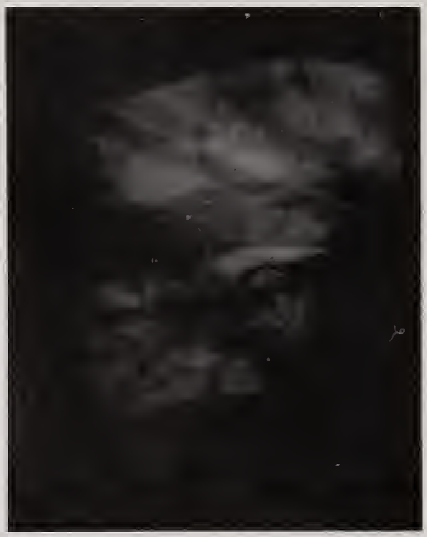

FIG. 3. Cineangiographic frame showing the wire loop snare encircling the fragment but not pulled tight.

Discussion

This represents the second time we have been asked to remove catheter emboli from the chest. The first also involved a central venous pressure catheter fragment which lodged in the right atrium[3]. Directness of route from the external jugular to the fragment allowed for prompt removal employing a rigid endoscopic forceps with alligator jaws (See reference). Dotter[1] summarized the available national literature on the subject and collected 29 cases of which, interestingly enough, six were reported from the District of Columbia. This has mixed implications; on the one hand attesting to the vigor and expertise of area physicians and their retrieval techniques, but on the other hand reflecting an inordinate number of iatrogenic mishaps. Of the 29 cases recorded by Dotter, 18 involved CVP

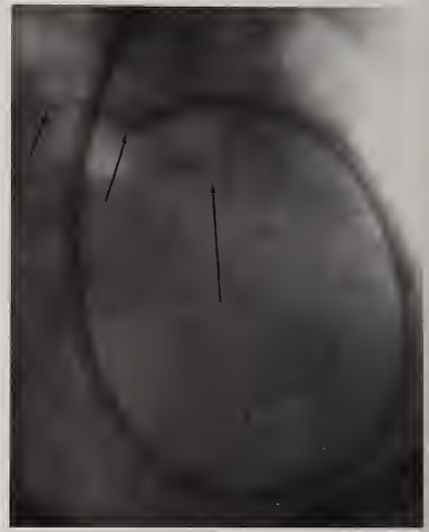

FIG. 4. Polyethylene fragment is now securely snared to the Cournand Catheter which has been pulled back to the main P.A.

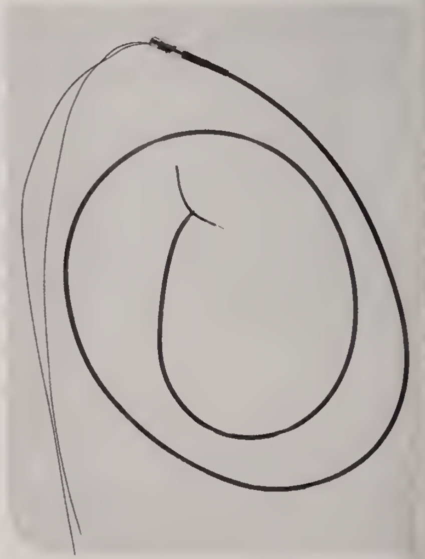

FIG. 5. Catheter fragment following removal, tightly secured to the Cournand Catheter tip. Note one inch of fragment had been removed for culture.

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*Cooke Incorporated 925 South Curry Pike P. O. Box 1272, Bloomington, Indiana 47401 TSF-25-260 Guidewire.

medical annals of the district of columbia

vol. 42 no. 3 march 1973

catheters and the longest fragment recorded was 40 cms.

Prevention

This increasingly frequent problem seems to be with us so long as aggressive intravenous monitoring and/or support is required until the present design of percutaneous intravenous equipment is modified. When using these systems, assiduous care should be taken to follow the accompanying instructions from the manufacturer, but even this does not insure prevention of tubing amputation. In the final analysis, house officers must appreciate the potential hazard of percutaneous jugular or subclavian catheter introductions and limit their use to only mandatory situations. Cardiologists as well as Surgeons must see to it that the materials and expertise are available for quick retrieval without resorting to thoracotomy.

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Treatment of Cardiogenic Shock*

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Although the treatment of cardiac arrhythmias following a myocardial infarction has decreased in-hospital mortality, cardiogenic shock remains a major cause of death. The mortality rate of cardiogenic shock is still in the range of 75 to 80%. It is estimated that over 100,000 individuals die yearly in the United States with this syndrome. The clinical profile of the patient with cardiogenic shock is familiar. At some point after sustaining a heart attack the blood pressure starts to fall and is usually no greater than 80 mm Hg systolic. A tachycardia of 120-140 beats per minute is quite usual. The skin color is a dusky cyanotic gray, and the patient is markedly diaphoretic. Urine output falls, and the patient's sensorium becomes clouded. He will often be barely arousable or may be quite irrational. Terminally, ventricular tachyarrhythmias or heart block may occur.

Many forms of therapy have been advocated, but the following seems to me to be most satisfactory.

The principles of therapy for cardiogenic shock follow from the pathophysiology of this condition. There is increasing evidence that the major factor leading to cardiogenic shock is an inability of the left ventricle to perform adequately as an effective pump. In almost all cases cardiac output is markedly diminished. Similarly, the hypotension which is a hallmark of this syndrome is in large part a consequence of low cardiac output. Since a critical pressure is necessary to maintain coronary filling, the hypotension has deleterious effects upon coronary filling, and this in turn leads to further deterioration in the ability of the heart to support the circulation. The two goals of therapy for this condition are: 1. To increase the cardiac output, and 2. to raise systemic blood pressure.

Both of these goals could be achieved if the left ventricle were helped sufficiently to augment its contractility.

General Considerations

Since cardiogenic shock has such a dreadful prognosis, any patient with this syndrome should be treated in a specialized facility capable of handling the intricate problems that arise. Adequate bedside and central nursing-station electrocardiographic monitoring should be available. An intravenous line capable of measuring central venous pressure should be present and fluids and medication may be administered through it. Although it is desirable under certain circumstances to be able to directly record arterial pressure through the use of a strain gauge and pressure transducer, this is not absolutely essential.

The measurement of central venous pressure may be important in unmasking hypovolemia as a contributory factor to the shock. With the widespread use of diuretics in cardiac patients it is not unusual for the patient who sustains a myocardial infarction to have the problems of hypovolemia added to those of pump failure. Although it is well recognized that the central venous pressure may be totally normal even if the patient is in pulmonary edema, knowledge of the central venous pressure does help management. If the central venous pressure is low or normal and if the patient is not in gross left-sided congestive heart failure with rales, dyspnea, and roentgenographic evidence of pulmonary edema, fluid therapy may be extremely valuable in reversing the state of circulatory failure. By taking advantage of the fact that as left ventricular end diastolic pressure and volume increase, so will left ventricular work and stroke output, a trial of 250 ml of isotonic saline or low molecular weight dextran may be tried. If this improves the circulatory state another 250 ml may be given. At times a simple therapeutic maneuver such as fluid administration may be of great help in relieving many of the manifestations of this syndrome.

If central venous pressure is elevated in the absence of cor pulmonale, there is generally little chance that fluid administration will be helpful, and the danger of causing pulmonary edema increases.

Other general principles such as oxygen administration and adequate pain relief will not be commented upon in this review other than to mention them. Pain, such as that which may occur with a myocardial infarction, may often lead to vagal reflexes which potentiate hypotension.

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Sufficient analgesia should be given to alleviate pain completely.

Digitalis Glycosides

There is considerable controversy concerning the role of digitalis glycosides in cardiogenic shock. The argument usually cited by physicians who are reluctant to use digitalis is the recognized potential of digitalis to cause ventricular arrhythmias. More recently it has been shown that any intervention which increases the velocity of myocardial contraction also increases myocardial oxygen consumption. One of the actions of digitalis is to raise the velocity of contraction, and therefore it may raise myocardial oxygen consumption. It has been demonstrated that areas of myocardium which are marginally oxygenated following an occlusion of a coronary artery may become necrotic instead of ischemic if myocardial oxygen consumption is augmented. However, if one accepts the thesis that the primary abnormality in cardiogenic shock is a marked depression of left ventricular contractility, digitalis therapy becomes a very rational means of trying to restore circulatory integrity. Unfortunately, a controlled study of digitalis therapy in cardiogenic shock is still not available.

It is my practice to administer digitalis early in the course of cardiogenic shock if the patient is not already taking it. The onset of action and peak effect of intravenous digoxin are such as to make it reasonable to use. Between 1.0 and 1.5 mg digoxin is given intravenously in approximately a two-hour period in doses of 0.25 mg every 15 or 20 minutes.

It should be noted that pulmonary venous congestion or other signs of left-heart failure need not be present in a patient with cardiogenic shock. I think, nonetheless, that digitalis plays a role in the therapy of the patient in cardiogenic shock. It should be stated, however, that this form of therapy is not agreed upon uniformly.

Vasopressors

The most easily recognizable feature of cardiogenic shock is hypotension. A variety of agents are available to raise the blood pressure. The sympathomimetic amines are often used. These drugs have been classified into alpha or beta stimulatory agents. Alpha adrenergic drugs act primarily on the peripheral arterioles and raise blood pressure by increasing peripheral resistance. Included in this group are methoxamine (Vasoxyl) and phenylephrine (Neo-synephrine). A second category of drug not only stimulates alpha adrenergic receptors in the peripheral arterioles but the beta adrenergic receptors in the myocardium. Metaraminol (Aramine), norepinephrine (Levophed) and epinephrine are examples. A sympathomimetic amine which has only beta-stimulating effects is isoproterenol (Isuprel). Since it acts as a peripheral vasodilator it does not appropriately fall into the category of a vasopressor, although it is a sympathomimetic amine.

Although raising the blood pressure is generally considered an appropriate goal in the treatment of a patient in cardiogenic shock, the issue is not quite that simple. Since most filling of the coronary arteries occurs in diastole, the coronary arteries require a certain level of pressure in the central aorta in order to fill. Myocardial function is dependent upon adequate coronary bloodflow and will deteriorate in the presence of inadequate perfusion pressure.

It has been shown that drugs which act only on the peripheral arterioles, thereby raising blood pressure by elevating peripheral vascular resistance, may have a deleterious effect upon patients in cardiogenic shock. If left ventricular function is sufficiently impaired to cause cardiogenic shock, increasing the resistance against which the left ventricle must pump may further decrease cardiac output. For this reason, drugs which act solely on the peripheral vasculature such as methoxamine or phenylephrine have little or no role in the therapy of cardiogenic shock.

Agents which act both on the beta receptors of the myocardium and the alpha receptors of the periphery have been used most extensively. It is wise to use as little of these agents as are necessary to maintain an adequate perfusion pressure, and it is also advisable to give these agents by intravenous drip rather than intramuscularly. By so doing, blood pressure can be titrated more precisely. It is not necessary for the blood pressure to be brought to normal levels. A systolic blood pressure of 90-100 mm Hg is usually adequate. It is my practice to place 50 mg of metaraminol in 500 ml of 5% dextrose in water. This is infused at a rate sufficient to elevate the blood pressure to the desired level.

Nor-epinephrine (Levophed) is another sympathomimetic amine which has potent effects upon both the peripheral and the central circulation. Although blood pressure can generally be raised by an intravenous drip of nor-epinephrine, experience indicates that relatively few patients survive if it becomes necessary to use this drug in order to sustain blood pressure.

Glucagon, a hormone which has been shown to raise blood sugar has also been utilized recently in patients with cardiogrenic shock. Although its mechanism of action is not known precisely, it does have the property of increasing cardiac contractility, possibly by augmenting the synthesis of cyclic AMP. Initial studies of this agent in the animal laboratory and in the human cardiac catheterization laboratory led to some enthusiasm for its use in patients with myocardial infarction and shock. Other than for some anecdotal reports of its efficacy this agent has been disappointing in the treatment of this condition and has generally been abandoned as a useful therapeutic agent.

Assisted Circulation

As indicated in Part I of this review, the major abnormality in cardiogenic shock is failure of the left ventricle as an effective pump. To this end considerable effort has been expended in the development of cardiac-assist devices to help the left ventricle which has been damaged as a consequence of a myocardial infarction.

Many lessons concerning prolonged assisted circulation were learned from surgical procedures utilizing extracorporeal circulation. Although the heart-lung machine may take over completely the functions of oxygenation and pumping of blood, there are many limitations to this technique for patients in cardiogenic shock. The need for a thoracotomy in a critically ill patient virtually rules out any potential efficacy of this approach. In addition, the problems of hemolysis, plasma protein changes, clotting, infection, and post-perfusion lung make prolonged extracorporeal circulatory techniques unfeasible for patients with cardiogenic shock.

Modifications of total extracorporeal circulatory assist have been utilized as temporary measures to help support a failing circulation. Veno-arterial pumping is one of these modifications. With this method, blood is withdrawn through a cannula introduced into the central venous system from the femoral vein and pumped into the arterial system. If the venous blood is passed through an oxygenator the patient is on partial heart lung bypass for all practical purposes. If no oxygenator is utilized, the procedure is much simpler but anticoagulant drugs still are necessary to prevent clotting within the system. It has been demonstrated that the lower body and extremities can tolerate prolonged periods of perfusion with venous blood.

Left-heart Bypass

This method of assisted circulation removes oxygenated blood from the left atrium and returns it to the systemic circulation. By so doing, flow to the left ventricle is diminished by the amount removed from the left atrium. The pump is in series with the right ventricle and lungs but in parallel with the left ventricle. By reducing cardiac inflow the distended left ventricle is given some degree of rest. It is likely that myocardial oxygen consumption is diminished as end-diastolic ventricular volume and radius are decreased. Left-heart bypass may be accomplished with or without thoracotomy. In cardiogenic shock thoracotomy is not feasible, but as an adjunct to postoperative care this method has been utilized with some success.

A method of left-heart bypass which does not require a thoracotomy has been developed. A transseptal cannula introduced into the external jugular vein is passed across the atrial septum into the left atrium. Although this method of cardiac assist was reported over 10 years ago, there is still no clinical trial demonstrating its efficacy for patients after a myocardial infarction.

Although any of these forms of assisted circulation reduce the flow work of the left ventricle, it has been demonstrated that myocardial oxygen consumption is much more closely related to pressure work. A method of assisted circulation that reduces the pressure work of the left ventricle should theoretically be of considerable benefit in reducing myocardial oxygen requirements.

Arterio-arterial pumping or counterpulsation is a form of assisted circulation that can reduce the systolic pressure against which the left ventricle must pump. In addition, counterpulsation raises aortic diastolic pressure and thereby increases coronary bloodflow. In 1961 Harken et al reported on a counterpulsation device which involved cannulation of the femoral arteries. By synchronization with the electrocardiogram the pump aspirated blood from the femoral arteries during cardiac systole and returned blood to the central circulation during cardiac diastole. Considerable diastolic augmentation was achieved. Other investigators, using synchronized counterpulsation in dogs, found that myocardial oxygen consumption decreased by over 20% and coronary bloodflow was increased by 50%.

A variation of the method of counterpulsation is that produced by the use of an intra-aortic balloon. This technique involves the inflation of the balloon at the onset of diastole and its deflation at the onset of systole. The advantages of this method are that it is totally intravascular and no blood is handled outside the body. There is less hemolysis in this technique than in counterpulsation devices which depend upon aspiration and return of blood to the vascular system for their hemodynamic effects. Heparin must be used, however, because of clotting of blood around the balloon. Rupture of the balloon with the introduction of gas emboli into the vascular system is a potential hazard. Damage to the aortic wall by overdistention of the balloon may occur. Although an arteriotomy must be made for introduction of the balloon into the vascular system, there is no need for the diversion of blood through a conduit of foreign material.

Because of the desirability of having a cardiac assist device which is completely non-invasive, counterpulsation with external body compression has been a goal of several groups of investigators. Such a device could be applied quickly, be free of any extra-

medical annals of the district of columbia

vol. 42 no. 3 march 1973

corporeal handling of blood, have no need for anticoagulants, and would not involve any operative intervention. Because of these features it might be available to a patient earlier in the course of cardiogenic shock before prolonged hyoperfusion of vital organs made survival unlikely. Counterpulsation of the extremities involves displacement of blood retrograde into the central aorta during diastole and increasing the capacity of the arterial system during systole so as to draw blood from the aorta.

Dennis and his associates utilized a pressure sleeve on the hindlimbs of dogs and applied synchronous counterpulsation. Osborn utilized a half-body pressure suit, but this was found to be uncomfortable when applied to normal volunteers. Keith found similar results in human volunteers. Soroff and his associates also evaluated external pressure suits with and without simultaneous external cardiac massage. The combination of external assist plus external cardiac massage was more successful in resuscitating dogs who were in ventricular fibrillation than external assist alone.

In 1968 a series of physiologic studies leading to the development of an external cardiac device called The Sequenced Pulsator was initiated by the author and several of his colleagues. The rationale of sequenced pulsation in contrast to nonsequenced external pulsation is based on theoretical considerations underlying the effect of externally applied pressure to vessels in the extremity. Large vessels with small wall thickness to lumen ratio more readily collapse in response to externally applied pressure than do smaller vessels which have a large wall thickness to lumen ratio. A uniformly applied external pressure to an extremity during diastole would therefore be anticipated to collapse the larger, proximal vessels first, thereby impeding return of blood to the central aorta.

The sequenced pulsator consists of arm and leg sections which are divided into multiple zones, each of which may be individually and separately activated to externally compress the enclosed body tissue. Activation is accomplished by inflating a chamber in each zone with compressed air. Flexible hoses connect the pressure enclosures for the arms and legs to the pressure and timing controller. The electrocardiographic signal from the patient directs the sequenced inflation of the zones through a series of solenoid valves. At the onset of the QRS complex, all pressure is simultaneously evacuated from the extremity cuffs. With such a mode the heart will never pump against a pressure wave produced by the assist device. The onset of cuff inflation can be set manually according to the length of cardiac systole. At the onset of cardiac diastole the sequenced pressure inflation is begun. By inflating the cuffs at the beginning of diastole, blood is returned to the central circulation with a consequent rise in central aortic pressure. When the ventricle contracts there is diminished resistance in the periphery due to the previous emptying of arterial blood into the central circulation during the previous diastole. Sequenced pulsation has a milking effect upon the arterial and venous beds as pressure is applied sequentially from more distal to proximal sites. Although the sequenced pulsator has not yet been utilized in the therapy of patients in cardiogenic shock, the preliminary laboratory results indicate that external sequenced pulsation can augment cardiac output and aortic diastolic pressure.

Circulatory assist devices have the combined aim of decreasing left ventricular work and also of increasing coronary bloodflow. By so doing it is hoped that a severely damaged left ventricle may be able to compensate and take over from the support device. Since cardiogenic shock is likely to be self-perpetuating once prolonged hypoperfusion of vital organs occurs, earlier application of assist devices may help some patients in cardiogenic shock. It must be recognized, however, that even with the early application of an assist device ischemic areas of myocardium may progress to the stage of necrosis. Acute re-vascularization of the myocardium with a saphenous-vein bypass graft may be helpful and necessary in selected cases. The role of the circulatory assist device in these cases will be to stabilize the patient while diagnostic studies such as selective coronary arteriography are performed. The success of this approach will have to be assessed as experience with spahenous-vein bypass grafting increases and the long range prognosis of the grafts becomes clearer.

Evaluation of Biologic Availability of Digoxin Preparations Available to a Naval Hospital

WALTER V. R. VIEWEG, CDR, MC, USN* AND JONAS SODE, CAPT, MC, USN†

Abstract

Four commercially available digoxin preparations, three in tablet form and one as elixir, were evaluated for biologic availability in four healthy subjects. The Burroughs Wellcome Company was the manufacturer of each preparation. Following a loading dose, serial serum concentrations and urinary excretion of digoxin were measured by radioimmunoassay. Although variations in the early absorption pattern occurred among individual subjects, the five-hour serum digoxin values were essentially the same at 0.5 ng/ml. Urinary recovery of digoxin was also similar among the preparations tested. These findings suggest comparable biologic availability for the preparations tested.

Prompted by the report of Lindenbaum *et al.*[1] that there exists significant variation in biologic availability of digoxin tablets, digoxin preparations obtained from the hospital pharmacy were evaluated. Most drugs available to Naval hospitals are originally purchased by a central agency which obtains them by way of a competitive bidding process. For the past several years the Burroughs Wellcome Company has been the manufacturer of the digoxin preparations distributed at the Naval Hospital, Bethesda, Maryland.

Subjects

Four healthy men, including the authors, whose ages ranged from 24 to 45 years, served as volunteers. All subjects were free of intestinal or renal disease. None were taking any medication during the testing period.

Methods

Digoxin preparations

The four digoxin preparations were all manufactured by the Burroughs Wellcome Company. Lot No. 377A (preparation A) consisted of .25 mg tablets contained in bottles of 100 tablets each. Lot No. 880A (preparation B) consisted of .125 tablets in bottles of 100 tablets each. Lot No. 592B (preparation C) was digoxin elixir, .05 mg/cc, in bottles containing 2 fluid ounces. Lot No. 048A (preparation D) consisted of individually wrapped .25 mg tablets.

Measurement of serum digoxin

Serum and urine digoxin was measured by radioimmunoassay using commercial reagents.[2] All samples were processed in duplicate. The labeled antigen was 3-0-succinyl digoxigenin tyrosine (^{125}I). Average recovery of varying concentrations of crystalline digoxin* from digoxin free serum by radioimmunoassay was 90%.

Absorption studies

Each of the four subjects was studied on four different occasions in an identical manner except that a different digoxin preparation was administered each time. Following an overnight fast, .5 mg digoxin was given by mouth at approximately 8 a.m. Blood samples were obtained before and at ½, 1, 1½, 2, 3 and 5 hours after the dose. The subjects were allowed to eat after the third-hour blood sample was obtained. Five-hour urine collections were obtained in 12 of the 16 absorption studies. Twenty-four-hour urinary digoxin excretion was determined in two subjects. Absorption studies were performed at intervals of a week or more. In each test, fasting serum was free of detectable digoxin. All subjects remained asymptomatic during each test.

Results

Table 1 gives serum digoxin concentrations following the oral administration of each digoxin preparation in

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department.

* Crystalline digoxin was kindly supplied by Stanley T. Bloomfield, M.D., Medical Department, Burroughs Wellcome Company, 3030 Cornwallis Road, Research Triangle Park, North Carolina, 27709.

TABLE 1. Serum Digoxin Levels Following Ingestion of .5 mg of Digoxin by Subject and Preparation

Preparation	Date	Time (hours)						
Subject V.		0	½	1	1½	2	3	5
A	17 Jan '72		.30	.80	1.10	.80	.60	.50
C	24 Jan '72	0	2.10	2.30	1.50	1.25	.80	.55
B	31 Jan '72	0	.25	.70	1.15	.75	.75	.50
D	7 Feb '72	0	.50	1.40	1.35	1.25	.95	.50
Subject F.								
D	17 Jan '72	0	.30	.40	.90	1.48	.75	.45
A	24 Jan '72	0	.63	1.33	.90	.70	.75	.55
C	31 Jan '72	0	3.30	2.17	1.15	.72	.52	.50
B	10 Feb '72	0	2.30	2.40	1.10	.80	.60	.50
Subject K.								
B	17 Jan '72	0	1.20	1.73	1.53	1.35	.90	.55
D	24 Jan '72	0	1.13	1.65	1.60	1.30	.90	.60
A	31 Jan '72	0	.50	.80	1.15	1.00	.70	.35
C	7 Feb '72	0	4.35	3.00	1.90	1.35	.55	.30
Subject S.								
A	17 Jan '72	0	1.08	1.28	.93	.88	.53	.48
B	24 Jan '72	0	1.43	1.40	1.00	.73	.60	.67
C	31 Jan '72	0	1.90	1.60	.95	.65	.35	.50
D	7 Feb '72	0	1.00	1.17	.85	.65	.50	.65

individual subjects. Mean values for each preparation are shown in figure 1. Statistical analysis by standard "t" test showed no significant difference ($p < .05$) between peak digoxin values, except for preparation D vs. preparation C (elixir) ($p < .05$) and preparation A vs. preparation C (elixir) ($p < .02$) (fig. 2). In comparing each preparation at each point on the absorption curve there was no statistical difference except for preparation A vs. preparation C (elixir) at 30 minutes and 60 minutes (both $p < .01$) and preparation D vs. preparation C (elixir) at 30 minutes ($p < .01$).

Urinary excretion of digoxin during the five-hour testing period was 18, 23, 26, and 31 micrograms for preparations D, A, B, and C, respectively. This represented approximately 4% for the tablets and 6% for the elixir of the loading dose. Approximately one month after these tests were performed, subject V ingested .5 mg of preparation C (elixir) and subject K, .5 mg of preparation B in the fasting state. Urine collection for the 24-hour period following ingestion contained .101 mg digoxin for C and .079 mg digoxin for B.

Discussion

The biologic availability of a pharmacological agent is an important factor in achieving and maintaining a desired therapeutic effect without the induction of undue toxicity. This is especially true for the purified digitalis glycosides whose toxic therapeutic dose ratio is low. Approximately 12-20% of hospitalized patients receiving digitalis are said to develop symptoms of cardiotoxicity.[3] Although electrolyte balance, oxygen tension, blood pH, and sensitivity of the myocardium and conducting tissue to the glycoside influence the frequency and seriousness with which digitalis intoxication develops clinically, variations in the biologic availability of cardiac glycosides in the dosage dispensed are equally important determinants of toxicity. A report by the National Center for Drug Analysis indicated that 47% of the batches of digoxin tablets tested did not meet the USP specifications of 92-108% of declared potency.[4,5] In addition, differences in biologic availability between digitalis preparations of comparable potency have been described, [1,6] these differences possibly resulting from interference with gastrointestinal absorption by inert materials incorporated into the tablets during the manufacturing process.[7] Prompted by these reports, we investigated our own sources of digitalis preparations.

Digoxin is the almost exclusive form of cardiac glycoside used in our hospital and the Burroughs Wellcome Company its manufacturer. Three of the digoxin preparations tested in this study were tablets and the fourth was an elixir. Peak serum digoxin values as well as serum concentrations at every point on the absorption curve for the three tablets tested were not statistically different and the similarity of the five-hour postabsorptive serum levels was striking for the three lots (figures 1 and 2). Digoxin elixir yielded significantly higher peak, 30-minute and 60-minute serum concentrations than preparations A and D. However, after 90 minutes serum digoxin levels following elixir and tablet preparations were again comparable. Urinary digoxin excretion over the five-hour period following ingestion of .5 mg digoxin was similar for the 3 tablet preparations tested and represented 4% of the loading dose. The five-hour

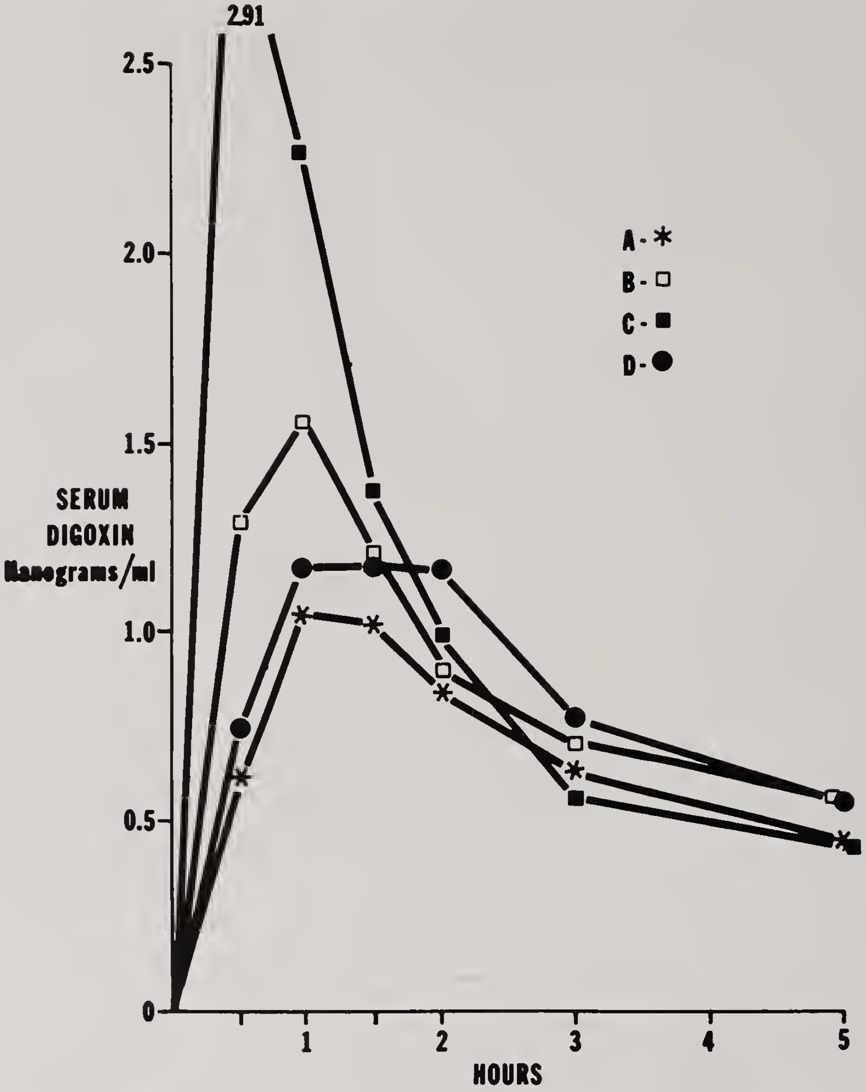

FIG. 1. Mean serum digoxin levels over a 5-hour period in four healthy men following the ingestions of .5 mg digoxin on four separate occasions using different preparations, three in tablet form and one in elixir form.

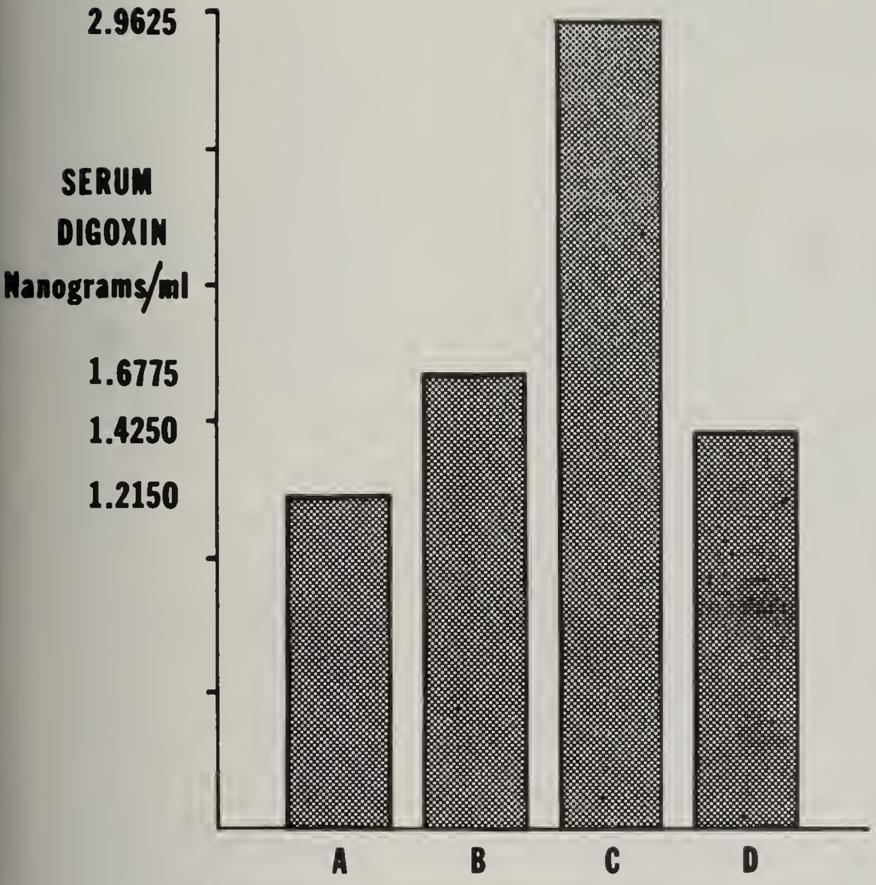

FIG. 2. Bar graft of peak serum digoxin values following ingestion of .5 mg digoxin for for each preparation tested.

urinary excretion for the digoxin elixir was 6% of the administered dose. Twenty-four hour urinary excretion was 16% of the loading dose for a digoxin tablet preparation (preparation B) and 20% for the elixir. These results compare favorably with those reported by Doherty where 16% of the loading dose of digoxin was recovered in the urine during the first 24 hours in 12 patients with normal renal function.[8]

Figure 3 compares our results with those obtained by two other investigators[1,9] who measured serum digoxin concentrations following the administration of 0.5 mg digoxin tablets manufactured by the Burroughs Wellcome Company. Our peak serum digoxin levels, although lower, are not statistically different from those obtained by Lindenbaum *et al.*[1] The five-hour postabsorption serum values for digoxin which presumably represent a developing equilibrium[9] between serum and tissue levels of the glycoside are strikingly similar for all three studies. A statistical comparison between our data and White *et al.*[9] was not performed. Urinary recovery of digoxin was not reported by either Lindenbaum or White and therefore a comparison is not possible.

Although the usefulness of serum and urinary digoxin measurements as indices of biologic availability require further investigation, the data presented here do suggest that the three tablets of digoxin manufactured by the Burroughs Wellcome Company exhibited acceptable and comparable biologic availability. Because of more rapid early absorption of the elixir and, possibly, greater total absorption, it is suggested that only with caution can the elixir and tablets be used interchangeably.

Acknowledgment

The authors wish to acknowledge the editorial support provided by the Clinical Investigation Center, Naval Hospital, San Diego, California.

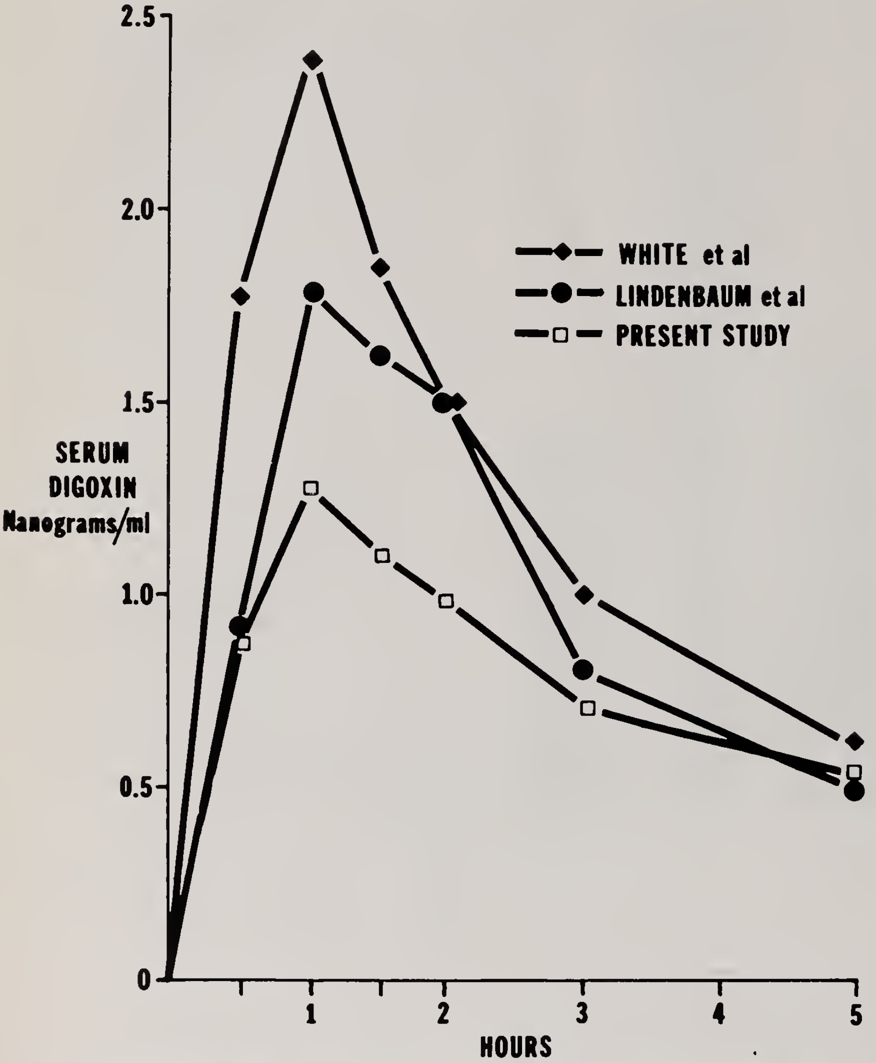

FIG. 3. Mean serum digoxin levels over a five-hour period following the ingestion of .5 mg digoxin in tablet form by three separate investigators using Burroughs Wellcome Company products.

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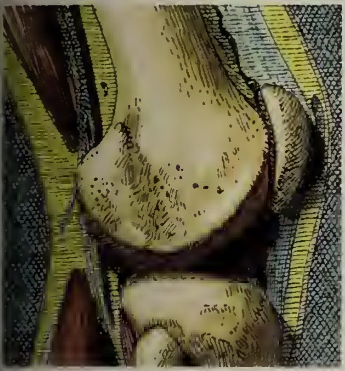
ERE Muscles and joints



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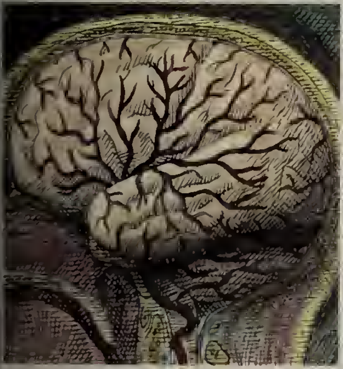

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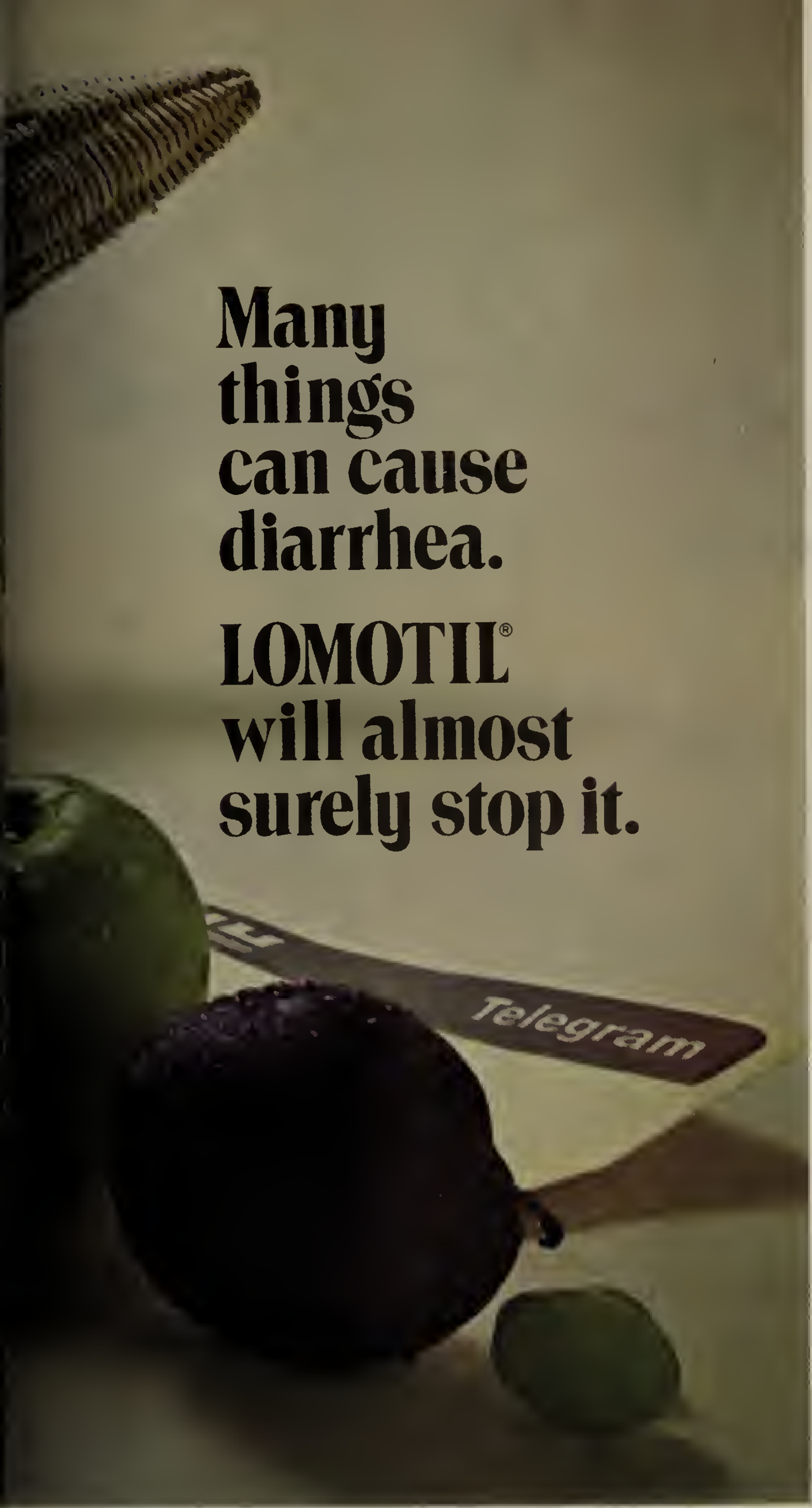

The causes of diarrhea are as varied as man's complaints and indiscretions. Because the causes of diarrhea can be obscure and because uncontrolled diarrhea can present serious problems, it is important to know a drug that will usually stop diarrhea promptly. For many physicians, the antidiarrheal drug of choice is Lomotil. It provides almost certain control of diarrhea.

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Effect on PBI Determination and I^{131} Uptake: Isopropamide iodide may alter PBI test results and will suppress I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.
Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.
Adverse Reactions: Drowsiness, excessive dryness of nose, throat or mouth; nervousness; or insomnia. Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).
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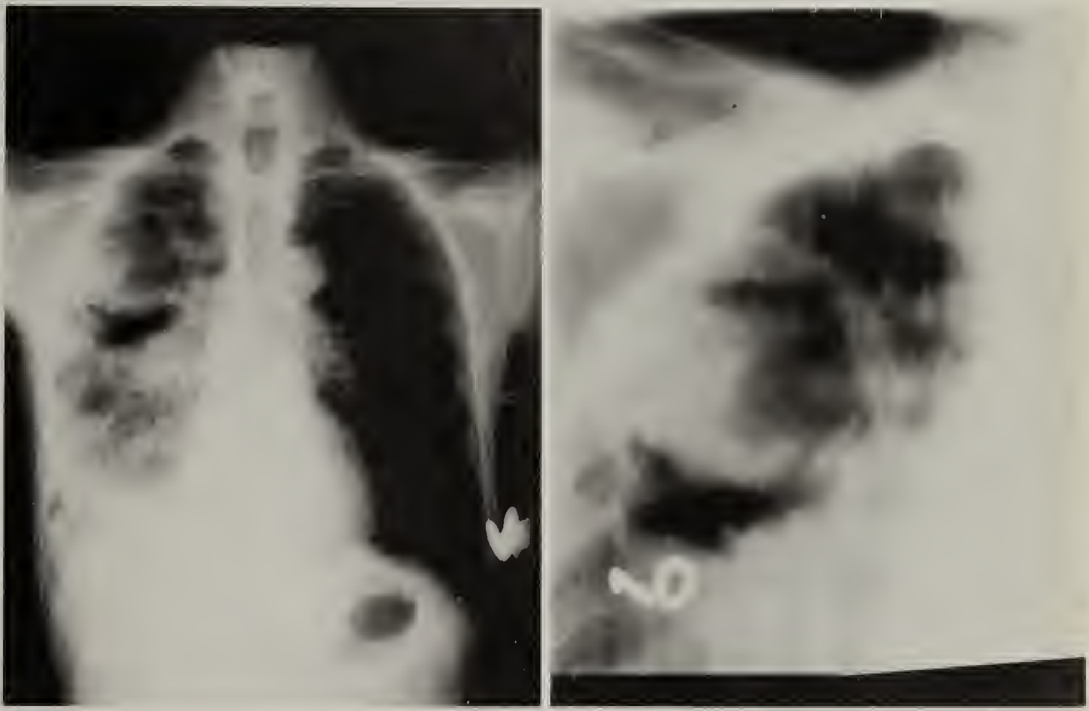
medical annals of the district of columbia

vol. 42 no. 3 march 1973

THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center



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(For diagnosis see page 156)

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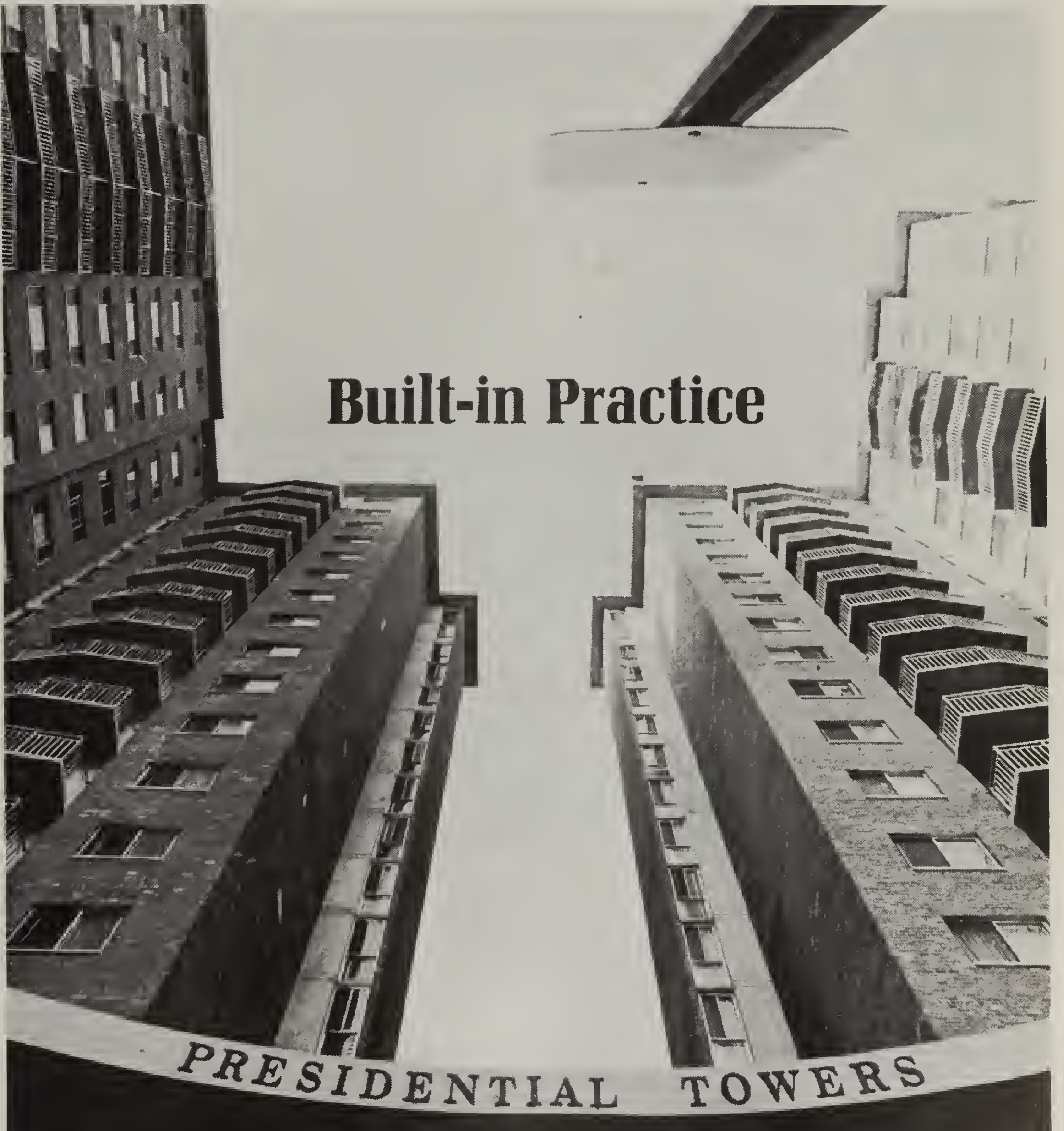

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Hematology. WILLIAM J. WILLIAMS, ERNEST BEUTLER, ALLAN J. ERSLEV AND R. WAYNE RUNDLES. Price, $32.50. Pp. 1480. New York: McGraw-Hill Book Company, 1972.

For many years, the "classic" text in this field has been Wintrobe's "Clinical Hematology." In these days of super specialization and rapidly expanding medical knowledge, one questions whether a single author can ever again encompass an entire discipline in sufficient depth to provide a source work in the field. Now, in addition to Wintrobe, we have an excellent book of multiple authorage. Most of the contributors are authorities in their particular areas of interest in hematology. Placed all together, they present the most comprehensive treatment of the field of hematology that is now available.

The organization of the text is superb. A detailed and extensive table of contents (169 chapters) enables one to focus down immediately on what one is looking up and go directly to it. The book is a compendium of specific topics in hematology—up to date and thorough in its treatment of each particular subject. The section on the erythrocyte is especially strong. It begins with Lawrence Lessin and Marcel Bessis' detailed description of the morphology of the red cell and is accompanied by many fine reproductions. It includes Richard Cooper and James Jandl on membrane defects, Ernest Beutler on biochemical abnormalities, Wendell Rosse on PNH, Scott Swisher on immune destruction, and Louis Wasserman on polycythemia. Turning to the white blood cell, there are up to date discussions of topics which are currently generating a great deal of investigative activity. These include granulocyte kinetics, the pathophysiology of phagocytosis, the biochemistry and function of the lymphocyte. Wayne Rundles and Frederick Gunz bring clarity to the confusing area of the myeloproliferative disorders. Other chapters worthy of special mention in this section are Jan Waldenstrom on "benign" hypergammaglobulinemia, Eugene Van Scott on mycosis fungoides, and Eliot Osserman on the plasma cell dyscrasias. The hemostasis section features summaries of the latest work in platelet phyisology and platelet disorders (qualitative as well as quantitative). There is a detailed yet clear exposition on the mechanism of coagulation and a "classic" article on a current topic, fibrinolysis, by Sol Sherry.

Added attractions for a work of this kind are chapters on the preservation of the different elements of the blood and their clinical usage in replacement therapy. Special mention should be made of the appendix; the various laboratory techniques described therein are an invaluable reference for the clinical hematologist seeking to interpret tests in the solution of diagnostic problems. The many fine color reproductions are, of course, an integral part of any book on this most visual of medical specialties, and further enhance its quality.

The book is primarily intended for the clinical hematologist, however, its discussions of current concepts provide ready sources of detailed information for the practicing internist or student of medicine as well.

HAROLD S. MIRSKY, M.D.

Current Pediatric Diagnosis and Treatment, 2nd edition. C. HENRY KEMPE, M.D., HENRY K. SILVER, M.D. AND DONOUGH O'BRIEN, M.D. Price $12.00. Pp. 1008 with illustrations. Los Altos, California: Lange Medical Publications, 1972.

This second edition of Current Pediatric Diagnosis and Treatment is so outstanding in many respects that it can be recommended highly to all health care personnel. Each of the 51 contributors have discussed clearly and concisely the common and uncommon but still important disorders and problems of children. The 40 very well organized chapters cover common pediatric diseases and various problems related to newborns and prematures, children who are ambulatory or in-hospital patients and adolescents. Comprehensive practical and didactic information for pediatric health personnel are found in chapters covering the history and physical examination, growth and development, nutrition, immunizations, neuromuscular disorders, developmental retardation, psychiatric disturbances, emergencies and accidents, poisonings and inborn errors of metabolism. Very useful and up to date information are found in the last five chapters on diagnostic and therapeutic procedures, management of fluid and electrolyte problems, drug therapy, chemotherapeutic agents and antibiotics, and most importantly, the meaning and interpretation of biochemical data and tests.

Very few criticisms can be made. The value of tetracyclines in treatment of erythema multiforme is questioned in children under age seven. In management of laryngotracheobronchitis use of racemic epinephrine is mentioned in table 12.3; however, nothing is mentioned about the efficacy of this mode of therapy in the text. Indications for use of steroids in management of hemangiomas is omitted. Use of steroids in children with toxic epidermal necrolysis is probably contraindicated. Management of urinary tract infections is clearly up to date, but use of nalidixic acid may be questioned. In discussion of essentials of diagnosis of atypical mycobacterial infections, one is rarely, if ever, able to elicit a history of the patients having contact with other persons with tuberculosis.

The compact and well organized style of this book with many excellent tables and figures as well as recent references at the end of each subsection and chapter, make this a very worthwhile text for all practicing physicians and nurses caring for children. The binding, flexible water repellent cover and low cost make this book very useful for medical students and residents. These readers would not hesitate to underline important data in the text or consider abstracting some of the complete tables of differential diagnosis and management of many rare pediatric disorders.

The chapter on ambulatory pediatrics is especially comprehensive providing many suggestions and practical methods including medical records (forms and flow sheets) for physicians, nurses and health personnel concerned with improving quality care to large numbers of ambulatory patients.

In summary this book will undoubtedly satisfy the pediatric text requirements of most medical students, many physicians in training as well as general pediatricians and family practitioners. It is not written for the pediatric subspecialist, however, physicians in other disciplines would benefit from its use as a concise, up to date pediatric reference which focuses on the principles of essential diagnosis and treatment.

ANDREW M. MARGILETH, M.D.

Air Pollution and Respiratory Disease. W. W. HOLLAND, Editor. Price, $20.00. Pp. 163. Westport, Connecticut: Technomic Publishing Company, Inc., 1972

This paperback book was edited by Dr. W. W. Holland, who is professor of Clinical Epidemiology and Social Medicine of St. Thomas's Hospital Medical School in London, with the assistance of five other British professors and one from Ireland. This was published under a grant from the United States Public Health Service and the Environmental Protection Agency of Washington, D.C. and is a credit to all concerned.

Despite the detailed attention paid in recent years to the problem of air pollution, little is so-far known of the *exact* relationship between pollution and respiratory disease. It is clear that populations exposed to increased levels of pollution, either during short-term or over a number of years—show an increased prevalence of respiratory symptoms and disease and an increase in mortality from respiratory causes; however, the role of *specific* air pollutants in the etiology of respiratory diseases has not been defined. This publication has two stated aims: First, to make a critical review of the relevant literature; and secondly, to evaluate current methods of investigation. A list of references follows each chapter and these are broad in scope and cover both British as well as United States and International references.

Most of the work discussed was carried out in Great Britain; this is obvious because of the author's first-hand experience. However, there are many other areas discussed including problems in the United States (e.g. pollution problems in New York, Los Angeles and New Orleans) as well as a discussion of the problems of Tokyo-Yokohama; and an excellent review of "Tokyo-Yokohama asthma."

One would expect such chapters as "The Measurements of Air Pollutants in Epidermatological Surveys" and "Problems Involved in the Measurement of Air Pollutants" which are well-discussed in this book, as well as discussions in field studies of respiratory disease morbidity and the importance of cigarette smoking. During all of these discussions the authors point out the *limitation* of our present knowledge and point out also the avenues of future research and understanding which are most helpful to the research oriented individual as well as to the practicing physician.

While none of us would be surprised by the chapter on "Air Pollution and Its Contribution to the Etiology of Lung Cancer," I was surprised by the chapters on "The Role of Infection and Air Pollution" and "Chronic Respiratory Diseases" along with excellent chapters on chronic bronchitis, emphysema, pulmonary hypertension and cor pulmonale; with excellent chapters on the pathology of these diseases.

As the authors so wisely state ". . . that in the planning of an investigation of the effects of air pollution, the epidemiologist must be aware of the functional and clinical disturbances of lung disease, both in early and late stages, and the exact relationship of this disease to air pollution is not yet defined." It is hoped that recent advances in respiratory physiology may enable the epidemiologist to study these changes in lung functions more effectively in the future.

There is also an excellent chapter on "Lung Function" and "Measurement Techniques" and the reasons for discussing lung function in some detail is that air pollution may cause lung disease and disturb its function and, measurement of lung function may demonstrate the ill-effects of air-pollution long before overt disease is apparent. In addition to the large list of references after each chapter, there are a great number of additional references listed as references not quoted in the text covering a great spectrum of pulmonary problems.

It is felt that this text should be on the shelf of every Public Health Official and should be a source of reference for our environmentalists and for any physician interested in our clean air problem. The chest physician, allergist and related specialists would benefit by a review of this excellent text and a follow-up on the references in relation to specific problems involved, I recommend this small reference volume for its specific as well as its general value to physicians as a whole, and hope that our Environmental Protection Agency officials have seen fit to read this text as well.

ALVIN SELTZER, M.D.

Should children be deprived of milk because of "lactose intolerance?"

No, according to the Protein Advisory Group of the United Nations.

In a special report, the PAG stated, "It would be highly inappropriate, on the basis of present evidence, to discourage programs to improve milk supplies and increase milk consumption among children because of fear of milk intolerance." The statement emphasizes that low lactase activity and results obtained in tests with high lactose loads are not adequate indications of milk intolerance.

The statement also affirms the advisability of using milk as an excellent source of protein in child feeding programs.

Dairy Council is sponsoring further research on lactose intolerance. This is just another of the many areas of interest of Dairy Council, in the pursuit of better health for everyone through sound nutrition practices.

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The New Hospital Psychiatry. GENE N. ABROMS, AND NORMAN S. GREENFIELD, Editors. Price, $10.00. Pp. 298. New York: Academic Press, 1971.

Of the various major psychiatric services, inpatient service has been the most discredited over the past two decades. Some have attributed much of the severe chronicity of psychiatric illness to hospitalization, and there are clinics that have a primary goal of avoiding hospitalization. Yet, many of the advances in psychiatry over these same two decades originated in psychiatric hospitals, and some of these advances can still only be provided in hospital or residential settings. *The New Hospital Psychiatry* reviews some of these advances.

This book is a collection of 17 papers presented at a conference held in 1969. As would be expected, these papers as a group lack cohesiveness, lack completeness and lack closure. Except for a comprehensive paper on psychopharmacology, the individual papers themselves present a smattering of ideas and observations with little attention to overall context in which the ideas and observations fit. Nearly all the contributors are teachers, and the education of the staff, education of students, and education of patients are major topics. A plurality of the papers focus on interweaving behavioral modfication concepts into the ward milieu, and the development of these concepts represents the book's major worth.

All the papers are clear and avoid jargon. Particularly, the two contributions by Abroms are refreshingly lucid. Any mental health professional familiar with psychiatric hospitals will find this book easy to comprehend.

Despite limitations and incompleteness, this book offers ideas and description of techniques for those in a position to improve the therapeutic effectiveness of a psychiatric ward's milieu.

ROGER PEELE, M.D.

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A Consumer's Dictionary of Food Additives. RUTH WINTER. Price, $3.95. Pp. 235. New York: Crown Publishers, Inc., 1972.

This extremely informative and very interesting soft-back book is, as the title states, basically a dictionary but it is packed with information for those who wish to fully understand the small print on the sides of the packaged foods in the supermarket.

Ruth Winter, an award winning science reporter, has written this dictionary primarily so that the laymen will be able to understand the nature of the mysterious ingredients listed on the food labels. Nevertheless, I feel certain that many physicians will also be able to benefit from the clear and concise definitions found in the book.

The introduction contains many facts of particular interest to those interested in the over-all area of food additives as well as the areas of food contamination and the loss of nutrients in the preparation of foods. These facts alone are eye openers and make the introduction alone well worth the entire cost of the book.

The additives themselves are listed alphabetically from Abies Alba Mill to Zingiberone. The definitions state where each item comes from, synonyms or other words used for the same additive, what it is made of, what it looks like, how it tastes, its additive function, what food or foods it may be used in, and whether or not it is toxic or beneficial. For each toxic citation, the source of the information is noted and listed in a separate section at the back of the book labeled "Note." The additives are also defined under certain broad categories such as whether they are preservatives, buffers, coloring agents, flavoring agents, bleaching agents or nutritional supplements.

The definitions themselves are clear and concise and most of the objections raised to certain additives seem valid. The texts cited in the notes as sources of toxicology are certainly authoritative texts.

This book is a must for any physician who is interested in the thousands of additives that are now available to us and can be especially recommended to the patient who is interested in knowing exactly what the food labels on the various food packages actually mean.

AARON G. SAIDMAN, M.D.

Application of Proteolytic Enzymes to Protein Structure Studies. ELEMER MIHALYI, M.D., PH.D. Price, $32.50. Pp. 364 with illustrations. Cleveland, Ohio: The Chemical Rubber Company, 1972.

The title of this book and the unique background of the author (research on actomyosin, digestion of myosin by trypsin and resistance of actin to trypsin, etc.) will probably not attract the practicing physician, but this combination is typical of an outstanding contribution to our modern scientific world. The book is published by the CRC Press (The Chemical Rubber Company) and is one of a series of great handbooks in biochemistry, bioengineering, chemistry, chromatography, electro-optics, engineering sciences, environmental sciences, food and nutrition, marine science, material sciences, mathematics and statistics, microbiology, organic chemistry, radiological sciences, spectroscopy and toxicology. These handbooks are not commonly found in a physician's office but knowledge of their existence should be of some concern.

The current book is a compilation of eight chapters by one author who attempts to fulfill a goal of providing a reasonably complete summary of the field of the actions of proteolytic enzymes on native proteins. This, of course, extends the problem to almost every facet of protein chemistry, involving a "wide variety of disciplines, from enzymology to physiology, immunology, pharmacology, and pathology, not to mention the more practical applications as, for example, food technology." The author believes it may be of some advantage to have all this reviewed by a single author, thus providing the opportunity for a unifying theme. A multiauthor approach, on the other hand, would lack continuity, suffer from redundancy, and would often reflect the authors' particular biases.

The text basically covers protein structure, proteolytic enzymes, enzymatic proteolysis, conformation and proteolysis, action of exopeptidases on native proteins, and the effect of endopeptidases on native proteins in limited proteolysis and in the formation of large fragments. This division of the text is superb, especially for a physician, because it would direct him immediately to the physiological section desired; e.g. effect of endopeptidases on

medical annals of the district of columbia

vol. 42 no. 3 march 1973

native protein as in conversion of fibrinogen into fibrin or the primary fragmentation of myosin by trypsin and chẏmotrypsin. In addition to the sections on fragmentation of proteins by enzymes, there is a small section on the fragmentation of the enzymes themselves, including cytochromes, catalase, escherichia coli-beta-galactosidase and diphtheria toxin. The section on immunoglobulins is of current value.

The book is well written and extremely well organized, and represents 26 years of uninterrupted research work by the author who is an expert in the field of proteolytic enzymes. It will be of value to a physician only if he is interested in detailed summary of this important field. The bibliography is intended to cover a fairly broad range but is incomplete; the author includes the main biochemical journals in English, French, and German from the period 1950 onwards; the Russion literature is not covered at all. Despite this, a physician will find the bibliography quite extensive and sufficiently complete.

The author is, at present, a chemist in the Laboratory of Biochemistry at the National Institutes of Health in Bethesda, Maryland.

A. EARL VIVINO, M.D., PH.D.

Handbook of Medical Treatment, 13th Edition. MILTON J. CHATTON, M.D., Editor. Price, $6.50. Pp. 648. Los Altos, California: Lange Medical Publications, 1972.

This handbook undertakes guidelines for the management of medical diseases; it is not all inclusive (nor is it meant to be), deliberately leaving out rare and obscure medical illnesses. There are 14 chapters, starting with General Symptoms, then Fluid and Electrolyte Balance, and concluding with Cancer Chemotherapy. An appendix discusses Heart-Lung Resuscitation. The genral format of each chapter is to describe briefly the illness and pathophysiology. Diagnostic details are omitted. Then acceptable medical treatments are concisely given and surgical indications when appropriate.

The author has obviously attempted to keep information updated by revisions every other year or better (13 editions in 23 years). Since there are no photographs and only a very few drawings or diagrams the size (and presumably the cost) of the book are minimized. Additional space is conserved by the elimination of all references. While this is an advantage for brevity, it offers no guide to the reader seeking further details of recent diagnosis and therapy. The greatest usefulness would most likely be to the medical student, intern, or resident and possibly the practicing physician to carry in his bag or automobile.

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Immunology, Immunopathology and Immunity. STEWART SELL. Price, $12.95. Pp. 277 with illustrations. Hagerstown, Maryland: Harper & Row, 1972.

The growth of basic immunology in the past 15 years and its application to clinical problems has been astounding. One has only to open any clinical journal to see how many articles are devoted to immunological causation of disease and to diseases of immunity. The rapid acquisition of so much information necessitates frequent review, condensation and synthesis of ideas. This accounts for the variety of new books about immunology such as Dr. Stewart Sell's, *Immunology, Immunopathology and Immunity.* This concise book aims to present the interrelations between these three aspects of the host defense system, stressing both its protective and destructive effects.

The first section, Immunology, deals with the basic principles of immune physiology. These include the nature of antigenicity, organization of immune cells and organs, antibody structure, antigen-antibody reactions and tolerance. There are brief descriptions of various immunological methods which help understand how this new information is derived. One could quibble about what the author chooses to stress and what he treats more casually. For example, one of the key current issues in immunology is the genetic mechanism of antibody diversity i.e. how the organism generates the multitude of different antibodies it needs for survival. This problem is given no more discussion by Dr. Sell than a description of the phagocytic index, a relatively unimportant method to measure the phagocytic capacity of an animal.

The section on Immunopathology summarizes how inappropriate immune reactions can cause disease. Allergy, immune complex disease, and collagen diseases are explored here. An expanded version of the Gell and Coombs classification of immunopathologic mechanisms is offered.

The last section, Immunity, shows the protective actions of the immune system against infection and cancer. Tumor immunology is one of the most important areas in immunological research these days. A measure of its growth is that all the newer texts are including this subject which hopefully will soon have clinical relevance. There is also a discussion of primary and secondary immune deficiency disorders.

This book is a useful, quick primer for the uninitiated in immunology. The illustrations are only barely adequate and sometimes confusing. In some places, photographs would have been more helpful than the drawings used. For the more serious student of immunology, even for most medical students, other recent texts would probably be more informative. This book has a place, however, for those wishing a brief introduction into the mysteries of the immune system.

DANIEL EIN, M.D.

THE VIEW BOX

(from page 145)

DIAGNOSIS: Cavitating bronchogenic carcinoma

The films show a thick walled cavity with many nodular irregularities protruding from the cavity wall. Almost the entire cavity is filled with a mass, partially free and partially adherent to the wall. There is no air fluid level.

The differential diagnosis to be considered in this case is cavitating carcinoma (often an epidermoid carcinoma) with necrotic parts of tumor in the cavity. Secondly, aspergilloma (fungus ball) in a pre-existing cavity of any type. The character of the cavity, thick wall (up to 1 to 2 cm.) and the nodularity of the wall should suggest carcinoma. Tuberculous cavities are usually smooth with a thinner wall and no fluid levels. These are often tension cavities. In a pyogenic abscess the wall is thick and the inner surface shaggy and often this is surrounded by a considerable pathological storm.

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McNEIL McNeil Laboratories, Inc., Fort Washington, Pa. 19034

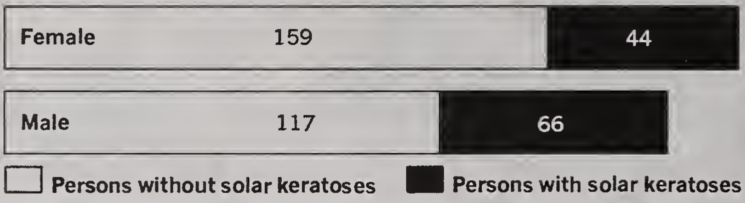
What it means to live and work i Tipton County, Tennessee

Persons who are white and over 40 have one chance in four of having solar keratoses... which may be premalignant

An epidemiologic study* conducted in Tipton County, Tennessee, revealed that 28.5% of white persons over 40 had solar keratoses; most had multiple lesions. Cluster sampling projected an estimated prevalence of 32.5% for white males and 19.5% for white females.

Though this is an unusually high percentage of affected persons, these lesions can occur in any white population, wherever people work or play out of doors.

Prevalence of solar keratoses in white persons over 40 in Tipton County, Tennessee



*Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey.

lar, actinic, senile keratoses

lled by many names, the typical lesion is flat
lightly elevated, brownish or reddish in
r, papular, dry, adherent, rough, sharply
ined; usually multiple lesions, chiefly on
osed portions of the skin.

quence/selectivity of response

thema in areas of lesions may begin after
eral days of therapy; height of reaction
ly in affected areas)* usually occurs within
weeks, declining after discontinuation of
rapy. Since this response is so predictable,
ons that do not respond should be biopsied
ule out the presence of a frank neoplasm.

smetic results

smetic results are highly favorable. Inci-
ce of scarring is low—important with multi-
facial lesions. Efudex should be applied
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ly Roche formulates the 5% cream...
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John B. Johnson, M.D.
1908–1972

Dr. John B. Johnson, Professor of Medicine at Howard University College of Medicine and Chief of the Division of Cardiovascular Diseases at Howard University and Feedmen's Hospital, died December 16, 1972. He resided at 1758 Shepherd Street, N.W.

He was born in Bessemer, Alabama, and received his undergraduate education at Oberlin College in Ohio. He received his M.D. degree from Western Reserve University in Cleveland and interned at Cleveland City Hospital. Following his residency at Freedmen's Hospital here, he joined the faculty of Howard University College of Medicine as an Instructor in Physiology and Pathology. He left for a time to study as a Rockefeller Foundation Fellow in Internal Medicine and Cardiology at Rochester University in New York.

He became Chairman of the Department of Internal Medicine at Howard University in 1949, which position he held until 1961.

An Active member of the Medical Society of the District of Columbia, Dr. Johnson was Immediate Past President of the Washington Heart Association and was also recently elected Vice President at large of the American Heart Association. He was a member of the American College of Cardiology and a Diplomate of the American Board of Internal Medicine. He was also active on program committees of the American College of Physicians. He had been President of the National Medical Association, and was Chairman of the Medical Section as well as Chairman of the Scientific Councils. He was also Governor of the D.C. Section of the American College of Cardiology.

Twice in the last ten years, Dr. Johnson was chosen as a member of teams of lecturers to visit South America, Indo-China and Africa, working closely with Dr. Paul Dudley White.

He is survived by his wife, Audrey Ingram Johnson, of the home address; two daughters, Linda Elaine Johnson and Adriene Renee Fairley; a step-mother, Mrs. Mary Johnson of Bessemer, Alabama; four sisters, Mrs. Cecelia Crum of Birmingham, Alabama; Mrs. Ann Nicholson of Detroit, Michigan; Mrs. Laverne Bembry of Salina, Kansas and Mrs. Roslyn Radden of Denver, Colorado; and two brothers, Dr. Walton Johnson of Philadelphia, Pennsylvania, and Samuel Johnson of Detroit.

Charles D. Lenhoff, M.D.
1912–1972

Dr. Charles D. Lenhoff, a Washington area urologist, died December 24, 1972. He resided at 2801 New Mexico Avenue, N.W.

Born in North Adams, Massachusetts, he received his B.A. and M.D. degrees from George Washington University and served his internship and residency at the old Gallinger Municipal Hospital here.

Dr. Lenhoff served with the U.S. Army Medical Corps in Europe during World War II and held the rank of Major. Upon leaving the Army in 1946 he entered into the private practice of Urology. He maintained offices at 1835 Eye Street, N.W.

An Active member of the Medical Society of the District of Columbia since 1946, Dr. Lenhoff was a past President of the Washington Urological Society. He was also a member of the American Medical Association and the American Urological Society.

He is survived by his wife, Davida Spund Lenhoff, of the home address; one daughter, Myra L. Wolf; two sisters, Ida Goldberg of North Adams, Massachusetts and Libby Waldman of Cohoes, New York. He is also survived by a brother, Samuel Lenhoff of Pittsburgh, Massachusetts, and two grandchildren.

Sterling V. Mead, D.D.S.
1888–1972

Dr. Sterling V. Mead, a retired dentist who had practiced in the Washington area for more than 40 years, died December 9, 1972. He resided at 721 South Peninsula Drive, Daytona, Florida.

Born in Stafford, Kansas, he received his D.D.S. degree from George Washington University here. He also held B.S., M.S. and D.Sc. degrees from Georgetown University. For four years he was a professor of radiology at George Washington University's dental school, and was associated with Georgetown University from 1928 to 1936. While at Georgetown he had been a professor of oral surgery, director of dental research and associate professor of anesthesiology.

Dr. Mead received many awards for his work in dental anesthesiology and research and for his service in the Naval Dental Corps during World War II.

The Mead Dental Hospital was in operation from 1959 to 1966 at 1401 16th Street, N.W. and was the first dental hospital here to be licensed and certified as a hospital, accepting in-patients for oral surgery requiring care for 24 hours or more.

For more than 30 years Dr. Mead was active in dental legislation. Primarily responsible for the District of Columbia Dental Law of 1940, he also worked for improvements in dental care given by the armed forces, for veterans and for dental coverage in the Kerr-Mills Act and for oral surgery coverage in federal employees legislation in 1962.

An Associate member of the Medical Society of the District of Columbia, he was former President of the American Dental Association and of the D.C. Dental Society. He was a Fellow of the American College of Dentists and of the International College of Dentists. He also was a member of the American Society of Oral Surgeons, and the American Society of Anesthesiology.

He received an alumni acknowledgment award from George Washington University in 1947 and in 1952 the honor award for achievement in Dentistry of Georgetown University's dental school.

He is survived by his wife, Neva Moxley Mead, of the home address; a son, Dr. Sterling G. Mead of Washington, D.C.; and five grandchildren.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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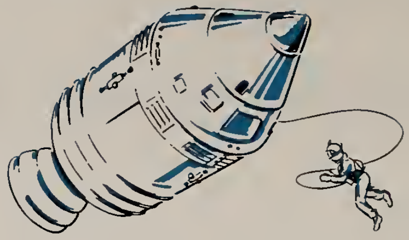

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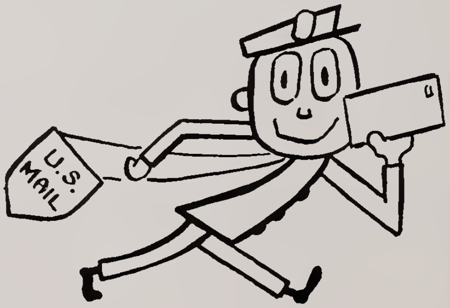

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Complications of Cardiac Pacemakers. Michael G. Seremetis, M.D., Vicente C. deGuzman, M.D., William S. Lyons, M.D. and Joseph W. Peabody, Jr., M.D. 165

Pseudoaneurysm After Angiography. Stanley Perl, M.D., Louis Wener M.D. and William S. Lyons, M.D. 173

Postoperative Abdominal Wall Necrosis. Charles W. Aaronson, M.D. 176

Primary Carcinoma of the Vagina. Case Report and Review of the Literature. Robert C. Hecker, M.D. 180

Sporotrichosis of the Thumb. A Case Report. Philip A. Cox, M.D. and Masud Homayouni, M.D. 182

Azotemic Malignant Hypertension: Clinical Course and Survival with Vigorous Antihypertensive Regimen and Intermittent Dialysis. Iluminado A. Cruz, M.D., Martin G. Dillard, M.D. and Adrian O. Hosten, M.D. 185

SPECIAL ARTICLES

Are Women's Fashions Necessary? W. Montague Cobb, M.D. 189

OTHER FEATURES

The View Box 172

EKG Problems 175

New Members 197

Book Reviews 201

Essentials of Roentgen Interpretation (Paul and Juhl) Reviewed by Gunter J. Augustin, M.D.

The Making of a Psychiatrist (Viscott) Reviewed by Robert E. Moran, Jr., M.D.

Differential Diagnosis. The Interpretation of Clinical Evidence (Harvey and Bordley) Reviewed by Lawrence E. Putnam, M.D.

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Dermal Pathology (Graham, Johnson and Helwig) Reviewed by Mervyn L. Elgart, M.D.

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Essentials of Cardiac Arrhythmias. Diagnosis and Management (Bellet) Reviewed by Alan M. Weintraub, M.D.

Obituaries 213

Information for Authors 20

Advertising and Subscription Information 20

Classified Advertisements 21

Index of Advertisers 22

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PRESIDENT'S MESSAGE

Irving Burka, M.D.

The News Media and the Doctor
"News—the Manna of the Day"

Several months ago, a series of articles about a large community hospital appeared in a local newspaper. In this series, several physicians on its staff were liberally quoted. Many of these quotes were critical of other departments, particularly one.

On investigation, it soon became very apparent that these gentlemen, all honorable men, were, on the whole misquoted. Many of their statements were taken out of context implying other than the original intent. There was no intention on the part of these physicians to harm anyone. None the less, several excellent and very competent colleagues were sorely aggrieved, and the department was nearly devastated by these words.

I mention this matter to emphasize that each of us is indeed a public relations representative of our profession, and should be always aware of this responsibility.

It would be the better part of discretion to refer any deficiency or ineptness in a department or an individual to appropriate committees of the staff. Certainly, the Medical Society and every hospital staff has built-in mechanisms for the correction of grievances, misunderstandings and incompetence wherever they may be found.

This, of course, is not meant to indict the Media. By and large the men and women reporters are honest and hard working, and usually are very fair in their reporting. They are, however, out to get a story. Their approach is of necessity different than ours. Furthermore, the fact is that the Government is the largest single purchaser of health care and the largest single contributor to hospital construction in our country. We are now truly in the Public Domain. The public wants to know and will want to be more informed about the activities of our profession.

When being interviewed, we should be certain that, we are in conformity with the code of ethics of our profession; we have all the facts; we attempt to know our interviewer and his motives; we limit criticism to our specialty or department.

Most of us are novices when it comes to this sort of situation and it is imperative to remember that there may be quite a slip between the lip and the printed page. It is well to understand with Wendall Philips that, "We live under a government of men and morning newspaper."

Quote:
The AMA doesn't represent me.
Unquote.

Maybe that's the way you feel. Thinking we do little to protect your way of life. Or that we don't share your views.

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Who did successfully testify against a headlong rush into a large-scale HMO program?

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Obviously, we can't represent the views of all physicians all of the time. But the goals we do share far outweigh any differences that may separate us.

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What the Government Bestows The Government Can Take Away

During the past decade American medicine has been increasingly and in many instances justifiably criticized for not providing equal health care opportunities to all citizens. The leader in making these accusations has been the Federal government. The effective and basically correct slogan has been: "Health care is a right, not a privilege". Flushed with the political pluses of the Medicare and Medicaid programs, federal officials have designed systems such as HMO's and have been increasingly critical of the medical profession for failing to implement such systems.

Approximately eighteen months ago the Nixon Administration found it necessary to move against the inflationary economic conditions by instituting Phase I controls. As we have passed through Phase II and now into Phase III, we know that the Federal Government has remained sufficiently alarmed at the high cost of health care, and as a result the health care industry remains one of only three industries still constrained by wage and price freezes (although the other two industries—food and construction—are not nearly as severely effected by these limitations).

Although the American Medical Association recently lodged a vigorous though self-serving complaint with the White House, it is not the largely fee-for-service physician membership of the AMA which is suffering so acutely under the continuing Phase III constraints as it is the hospital institutions in the United States, many of which serve as the focal point of health care delivery to those citizens of lower socio-economic status, particularly in the urban areas of our society. Traditionally, the delivery of medical care to the medically indigent has been a "loss leader" in hospitals, and, despite some lessening of the burden by Medicare and Medicaid, the fiscal losses have in the past been made up by voluntary hospitals by increased charges placed against the self-pay patient or the private health insurance carriers.

Now health insurance carriers, in particular Medicare, refuse to subsidize indigent care programs. Hospitals, if prior recipients of federal Hill-Burton construction funds, have been instructed by an HEW directive in early 1972 that they must donate services to "charity patients" up to 3% of their gross operating costs. The continuing Phase III constraints have placed the hospital in precarious financial circumstances, and after allowing permitted 5.5% salary increases to all institutional employees, hospitals are undergoing drastic budgetary trimming for 1973 and possibly beyond. As one is forced to trim a hospital budget, the eye quickly falls on such costly losing items as delivered care to the medically indigent (locally, the D.C. Medical Charities Program), and the natural result in hospitals experiencing such budgetary limitations is reduction in services to this group of community patients to as close to the aforementioned 3% limit as possible.

So what happens? Simple! Locally, the "second class medical citizen" receives less than adequate attention at the hospitals, or is turned away to disappearing outpatient public health facilities, or if hospitalization is warranted is transferred to D.C. General Hospital, where in this soon to be even more over-crowded facility at least medical care is reimbursed at full cost through D.C. Government and federal funds. Therefore, under the present circumstances, medical care is again becoming a privilege!

Despite all the outcries from legislators, despite the newspaper crusades against hospitals, the only final way in which our health delivery system can comply with the correct and reasonable demands of our society is to obtain adequate reimbursement of the cost of these services. Yes, that will carry a very large price tag. But to continue to squeeze health care institutions between demands for quality care for all citizens and inadequate financial reimbursement is totally unrealistic and is presently causing reduction in our services to those patients who identify with hospitals as their primary source of health care.

The government can bestow with one hand, and the government can take away with the other hand. And the result is intolerable.

Louis Gillespie, M.D.

Hasty Health

Some time ago we received at home a notice, bureaucratically concise as only government notices can be, that all children were required by Maryland law to be immunized against Rubella. I must confess to some considerable chagrin at that notice. And almost embarrassment. After all, objecting to such an obviously well-meaning law seemed almost like coming down on the wrong side of the fluoridation controversy. But not quite. Here we are being told that an entire population is to be given a relatively new immunization in order to prevent a disease that is hazardous to one-half of the population. It just seemed wrong-headed. And this is not in any way to be interpreted as an attempt to minimize the seriousness of the Rubella problem. But, speaking both as a parent and as a physician, and particularly in these times of increasing awareness of iatrogenic diseases, there must have been a better way.

However, like most good citizens, we comply with the program. The experts must certainly have considered these factors. Surely there must be incontrovertible evidence that herd immunity will be induced, just as in Sabin polio immunization. There must be good statistical evidence that this mass immunization of males and females would indeed eradicate Rubella more quickly than any alternative approach.

Yet now we read a report from Wyoming entitled "Failure of Rubella Herd Immunity During Epidemic".[1] The report suggests that the mass immunization approach may not be as effective as had been hoped in preventing Rubella epidemics. While the study is small and imperfect, it certainly suggests the possibility that all those little boys might indeed have been immunized in vain.

In an editorial in the same journal, the concluding statement is, "Although immunization of small children may not be given up, it strikes us that laws to make immunization against Rubella compulsory that have been passed in some parts of the country cannot be defended and should be repealed. Serious consideration must again be given to the recommendations made by some that immunization against Rubella be concentrated in pre-pubertal girls and in women, known to be non-immune, immediately after the delivery of a child".[2]

Physicians are sometimes accused of being too conservative. Here again we have an example in which medical officials and supporting legislators in their desire to accomplish a great good in a short period of time might have done more good with a more conservative approach.

Paul Schlein, M.D.

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Denial of Insurance Benefits

The retroactive denial of benefits for hospitalization and physicians' services is one of the most serious problems facing patients, physicians, and hospitals at the present time.

The classic example is that of the elderly Medicare beneficiary who is admitted in serious condition after a stroke. It is only several weeks after discharge that the patient (or his family) is notified that the carrier has denied benefits for some part of the hospitalization on the grounds that care was only custodial at that time. Then the patient, who had thought himself adequately insured, finds himself solely responsible for hospital and physicians charges for that portion of his hospital stay.

Similar problems exist with regard to benefits for private duty nurses. No practicing physician is unaware of the difficulty involved in trying to justify private duty nurses for a patient who may have been discharged weeks or months before the carrier requests justifying statements.

Should these sound like isolated and infrequent occurrences, then check with your colleagues at staff meetings, in doctors' lounges and at Medical Society meetings. You will probably discover that entire admissions are being categorized as unnecessary and thus uncovered. This occurs particularly in the area of admissions for obesity, hypertension and gastrointestinal complaints.

As with any problem a reasonable man can see some virtue on either side of the question. Certainly, an admission for abdominal pain of brief duration which results in a barium enema on day two, an upper GI and gall bladder study on day three and discharge on day four is highly suspect. The medical reviewer can justifiably say that most people practicing good medicine would conduct that work-up on an outpatient basis.

On the other hand a patient may be admitted with a complex illness requiring a long hospitalization. That hospitalization may be approved in an on-going fashion by the hospital utilization committee and yet some part of it may be still turned down for benefits by the carrier.

What is the solution to the problem? The first approach, of course, lies in the hands of the physician. He should be critical about the types of problems he admits to the hospital. Once the patient is in, the physician should be equally critical about the length of stay; neither cutting it short to the patient's detriment nor prolonging it for the patient's convenience.

For their part what can the carriers do? In my view they can do something of a positive nature instead of adopting their current negative stance of retroactive denials which only serves to alienate patients and physicians and give private insurance a bad name.

They could set up pre-admission review in totally elective cases.

They could set up utilization review which would review within 48 hours of admission and make a recommendation regarding justification to patient, physician, hospital and carrier.

They could pay physicians to do ongoing utilization review in hospitals and demand more critical and more up-to-date review than is usually done now.

They could take the unpopular stance of publicizing some of their non-covered services instead of leading patients to think that hospitalization means automatic payment.

They could do many things in concert with the participating physicians if both sides are truly interested in perpetuating private health insurance.

If either party doesn't have enough interest to do this difficult job, then the disillusionment of the patients will enhance the position of the proponents of a national health scheme. I am convinced that, apart from catastrophic coverage, the private sector can do the job better than can the federal government. Not the least of the benefits of the private approach is the curtailment of further proliferation of the federal bureaucracy.

Robert W. Langevin, M.D.

What has Happened to the Fine Art of Consultation?

One of the distressing events, it seems to me, is the gradual decline of the art of requesting a consultation. In years gone by, consultations were held by appointment at a specific location by all of the physicians in attendance with a given patient. The chart was reviewed as well as appropriate X-rays and the patient was then visited by one and all. Very often the residents, nurses and medical students were in respectful attendance.

After the patient had been examined, the physicians retired to the consultation room and mapped out a plan of strategy. Following this, the senior attending physician and consultant would return to the patient's room and give the report to the patient and often the family as well.

Contrast that with the present day method of obtaining a consultation. Times have changed, obviously, and we need to keep up with them, but in this case, I wonder why. It is true that physicians are busy and harried, nurses and receptionists become short-tempered with the press of work, and the pace of life has quickened.

One must deduce that it has become difficult for the physician to contact his consultant and arrange for a visit to review X-rays, charts and other data. It is horrible to relate, but there are actually instances in this metropolitan area every day where a nurse or station attendant calls a physician's office and relates that Dr. So-and-So has written an order on the chart requesting that Dr. So-and-So be called in consultation for such-and-such a patient. And as you would suspect, the consultant, upon calling back to the Nursing Station, often in a pique of rage, learns that the nurse knows nothing about the case.

There is a happy balance which most of us have resorted to without too many feelings being hurt. That is this. The physician usually contacts the other physician, either in person or over the telephone and discusses the entire case with him. X-rays and other data are reviewed later by the consulting physician. This will often involve talking with the residents, nurses and often technicians. Only rarely, it seems to me, do physicians get together for a visit at the patient's bedside. But this level of consultation has gradually been reached without too many bruised feelings, and in fact, with a remarkable degree of efficiency. The consultation note is dutifully placed on the chart; very often the referring physician is contacted by telephone and again, quite often, a report is sent out immediately. Of course, there are some physicians who never bother to send a report and scribble an illegible note on the chart. But at least they have the rudiments of the right idea.

But it is to those physicians who callously request the consultation on the order sheet to whom most of our ire is directed. It might be that a few pointed comments by the various chiefs are in order. It may help. Certainly the denim trousers, khaki slacks and Shiloh look are on the wane. Things may be looking up.

John M. Keshishian, M.D.

For an organization supposedly opposed to change, the AMA has made a lot of changes.

One of the most significant was the addition of an important new voice in the AMA—that of interns and residents. For the first time, these young physicians have not only a voice but also a vote in helping shape AMA policies.

Recently, the AMA House provided the same opportunities for membership and participation to medical students.

That's not all. In another important change, the AMA's council-committee structure has been streamlined. Some councils and committees have been dropped. Others have been made more efficient by reducing their size to seven members for councils and five for committees. And to permit more frequent infusion of new members and ideas, maximum tenure of service has been reduced to seven and five years, respectively.

The AMA *has* made a lot of changes. Changes to make it more responsive to the ideas of *all* physicians . . . changes to make it more effectively serve the needs of the profession.

Change will continue. But it will be decided only by those of you interested and dedicated enough to be a force in that change.

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Complications of Cardiac Pacemakers

MICHAEL G. SEREMETIS, M.D.*, VICENTE C. DEGUZMAN, M.D.†,
WILLIAM S. LYONS, M.D.‡ AND JOSEPH W. PEABODY, JR., M.D.§

During the last 15 years, since the development of effective and practical pacemaking devices, there has been a dramatic change in the outlook for patients with heart block. Not only has their survival rate been improved, but the quality of life for these patients is closer to normal. They are able to conduct normal physical activities, and most of them actually "forget" the presence of the implantable device inside their bodies. Many patients describe the "new life" and "new strength" that come after the insertion of the pacemaker. Others recognize how restricted their activities had been and how frightened they were about falling, convulsing, or fainting.

Everyone has had disappointments and frustrating, unexpected failures and complications, especially during the initial years.[1-10] With improvements in instrument technology and in surgical techniques, the incidence of complications has been reduced; nevertheless, we need further improvements to make the whole procedure safer, more reliable and easier for the patient.

This paper deals with the incidence, recognition and management of various complications during a ten year period, in 490 patients seen by us at various hospitals in the Washington metropolitan area.¶

Materials and Methods

This series includes 490 patients who needed artificial pacemaking between 1962 and 1972. Three hundred forty-two patients received 570 permanent units. One hundred forty-eight patients were paced only for short periods of time. One hundred sixty-two patients were first paced temporarily, and then they received implanted permanent units.

All patients received Medtronic equipment. Initially fixed-rate models were used. The demand stand-by type (R-wave inhibitive type) has been used increasingly since 1968, and it is used almost exclusively now.

The mean age of the patients was just over 70 years; the age range was from 38 to 92 years. The mean age of the patients who received temporary pacing only was slightly less—67 years. The sexes were almost equal with slight preponderance of males.

The indications for artificial pacemaking were as follows:

80%	were patients with complete heart block with or without Stokes-Adams syndrome,
11%	had persisting heart block after myocardial infarction,
9%	had either sinus bradycardia or variable heart block.

The indications for temporary pacing were:

55%	intermittent or transient heart block following myocardial infarction,
25%	Stokes-Adams syndrome not controllable with Isuprel as an emergency preliminary procedure,
11%	unexpected pacemaker failures with recurrent syndrome,
4%	effort to control certain tachyarrhythmias,
5%	to evaluate the possible benefit of pacemaking.

In 30 patients who required permanent pacing, epicardial electrodes were sutured on the myocarcium. In 26 of those cases (mainly during our initial years) this was done through a left thoracotomy. In four of those cases a transdiaphragmatic exposure of the heart was accomplished through an upper midline laparotomy. Our preferred approach now is the endocardial transvenous route through the cephalic or jugular veins. This procedure was performed 316 times. Four patients had endocardial electrodes inserted first and then epicardial ones, as will be mentioned later. The temporary electrodes were usually inserted through a cut-down in the antecubital area. In a few emergency cases, the jugular system was used. All the transvenous electrode insertions except 30 were performed under fluoroscopic control. In those 30 cases temporary electrodes were inserted blindly with EKG monitoring, in critical patients who could not be moved out of the coronary care unit.

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¶ Washington Hospital Center, Morris Cafritz Memorial Hospital, Sibley Memorial Hospital, Doctors' Hospital of Washington, D.C., Suburban Hospital in Bethesda, Md., Holy Cross Hospital in Silver Spring, Md., Washington Sanitarium and Hospital in Takoma Park, Md., and Prince George's Hospital in Cheverly, Md.

Results, Complications and Management

The improvement in the cardiac, mental, and general condition of patients after successful implantation of a pacemaker has been uniform. When the system remained intact and functioned normally there was not a single instance of recurrent Stokes-Adams syndrome. The subjective improvement of patients was often dramatic. Some of them stated that they were feeling better with the pacemaker than they had felt during the preceding 5 or ten years.

There have been various complications. We have divided them into operative, early post-operative, and late post-operative complications. Table 1 lists all the complications that we encountered.

Operative Complications and Management

During the procedure the most serious and dangerous complication is development of cardiac arrhythmia, especially ventricular fibrillation and less often asystole. Nine patients developed this complication and all were successfully resuscitated. No deaths occurred in the operative period. The management of fibrillation or asystole is a routine measure in cardiopulmonary resuscitation. Careful preparation of the patient is important. Adequate personnel, proper equipment, and drugs must be available in the operating room in anticipation of these complications.

We routinely perform pacemaker implantations under local anesthesia, but we always have an anesthesiologist present. He establishes an intravenous infusion. He can, if necessary, ventilate the patient with or without endotracheal intubation.

Occasionally there has been difficulty finding a suitable vein for catheterization. We prefer the cephalic vein; but if it is not satisfactory one can use another tributary or even the subclavian vein itself. The jugular veins are the second choice. In emergency temporary insertions, especially if the procedure must be performed in the coronary care unit instead of the radiology department, the internal jugular is the best direct route. It was used successfully in six instances in our series.

TABLE 1: List of Pacemaker Complications

I. Intraoperative
  A. Arrhythmias (Asystole-Ventricular Fibrillation)
  B. High threshold
  C. Difficulty to find suitable vein or pass catheter
  D. Misplacement of catheter into coronary veins
II. Early Postoperative
  A. Hematomas
  B. Infections
  C. Hiccoughs
  D. Myocardial irritability
  E. Perforations, right ventricle
  F. Loss of electrode position
III. Late Postoperative
  A. Wire breakage
  B. Late infection
  C. Thrombosis of veins
  D. Inability to remove catheter
  E. Runaway
  F. Dehiscence of wound
  G. Premature failure of Pulse-Generator

In exceptional cases there may be difficulty in pacing the patient even if the electrode tip seems to be in perfect position. Our series includes two such patients with very high thresholds. The only way to pace them was to use a high output pacemaker unit. Both patients were maintained with these units; but they required more frequent replacement of the pulse generators, because their energy supply was exhausted sooner.

Another operative complication is misplacement of the tip of the electrode into the coronary sinus. The fluoroscopic appearance in the anteroposterior projection is about the same whether the tip lies in the right ventricle or in the coronary sinus. Certain signs are helpful in making the distinction: the development of premature ventricular beats, the lower threshold necessary to produce capture, and a lateral X-ray. Misplacement of the electrode into the coronary sinus occurred twice in our series. Both patients paced well for two and one half weeks. When their pacing became intermittent our suspicion was confirmed by a lateral X-ray of the chest. Repositioning of the electrodes into the apex of the right ventricle was necessary in both instances. Since then, lateral X-ray has become routine.

Early Postoperative Complications

There were six instances of hematoma in the subcutaneous pocket containing the pulse generator, and four of infection, all within eight days after implantation. Hematomas are preventable by careful hemostasis and by routine drainage of the pocket through a separate stab incision. We prefer to insert a urethral catheter and connect it to low suction. It usually can be removed within 24 or 48 hours.

One patient developed not only extensive hematoma, but also a large area of ecchymosis from an unexplained bleeding tendency.

Infection must be prevented by very careful aseptic technique. In addition all our patients are given intravenous antibiotics (preferably cephalothin) for two days, and then oral antibiotics for one week.

Hiccoughs and some diaphragmatic clonus were observed in five patients soon after insertion of the pacemaker. The contractions subsided within four days without treatment, except in one patient who required relocation of his electrode catheter after a few weeks. The diaphragmatic contractions were not connected with perforation of the right ventricle. In every instance the tip was lying low against the diaphragm, a position present in many other patients who did not develop hiccoughs or clonus. Interestingly, the phrenic nerve was not in close proximity in these patients. It is important to recognize the relationship of pacing to the actual diaphragmatic contraction. There were two patients who complained of a feeling of "kicking" after pacemaker implantation; but electrocardiographic monitoring demonstrated that both were not pacing at the time and simply had palpitation. One often can feel the diaphragmatic clonus by placing his hand against the hypochondrium and simultaneously observing the electrocardiogram.

Irritable myocardium with frequent premature ectopic beats was seen in ten patients. Many others showed occasional premature contractions. Lidocaine administered intravenously effectively controlled the ventricular hypersensitivity within a few days in all but two patients who continued to exhibit premature contractions for several months.

Perforation of the right ventricle (Fig. 1) resulted in loss of pacing but no tamponade or other serious complications in three patients. Two of them had perforation by temporary wires, and one patient had perforation by a permanent bipolar one. All occurred and were recognized within four days after surgery. Simple withdrawal of the offending electrode and careful repositioning was effective in all instances, except one that required epicardial electrodes (Fig. 1). The perforations were strongly suspected from the radiologic examination of the chest.

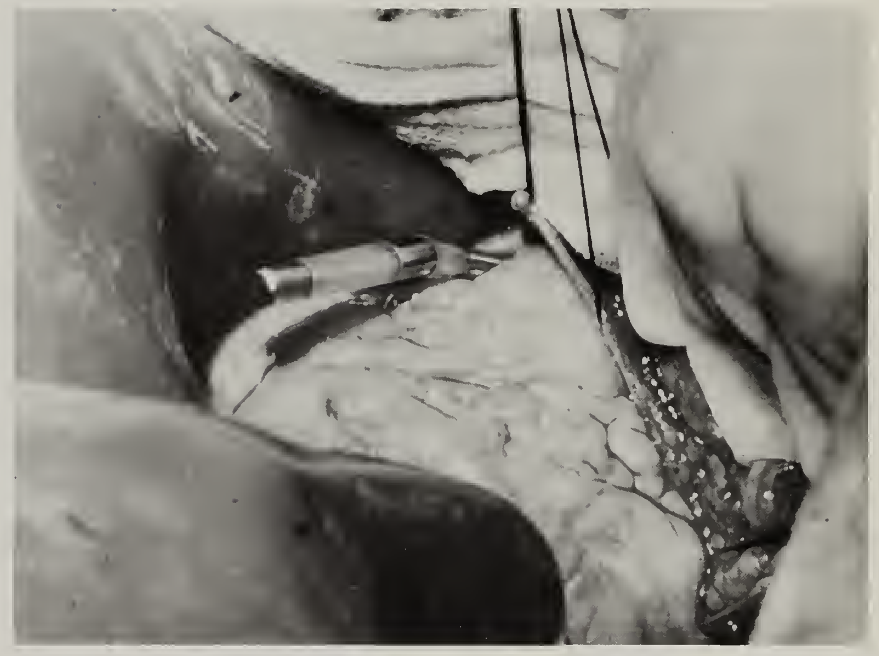


FIG. 1: Perforation of right ventricle in a 64-year-old, white man who required epicardial electrodes. Operative photograph.

The most common early complication in our series was loss of position of the electrodes. Occasionally, this occurred as a late complication. It happened 18 times after 316 insertions (5.7% incidence). All but two were dislodged within five days after surgery. The remaining two lost their position five months (Fig. 2) and 28 months postoperatively. Two patients required more than one repositioning: one three times, the other four times. All these positions were unstable, so epicardial electrodes were inserted. The other 16 patients did well after a single adjustment of the catheter position. None of the epicardial electrodes

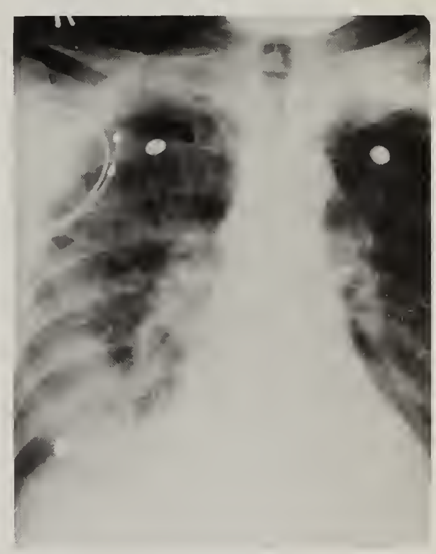


FIG. 2: Displacement of endocardial electrode and its almost complete withdrawal in a patient 79 years old who had original implantation five months prior to this time. Patient became very active after initial treatment with pacemaker and almost fainted after a session of push-ups. X-rays revealed the displacement. All transvenous catheters were tied with heavy, non-absorbable material at least in two areas close to the venous insertion.

were displaced after being sutured onto the myocardium.

Late Postoperative Complications

Wire breakage occurred ten times in our series, from three to 35 months after implantation (Figs. 3 and 4). Seven of the 316 endocardial catheter wires broke (2.2% incidence). Three breaks occurred in the 30 epicardial electrodes (10% incidence). With one exception, the breaks occurred near areas of angulation. That one exception resulted from direct blunt injury to the chest when the patient tried to push his stalled automobile. With two exceptions, a break in the continuity of the wire was manifested by loss of pacing. Two myocardial electrodes have broken within the myocardium without loss of capture. In one case a broken wire was found after loss of pacing; but at exploration we found that a loose lead, not the broken wire, was responsible for nonpacing. Two additional cases showed acute angulations and probable impending breaks, so the electrode wires were relocated surgically.

With one exception, all wire breaks occurred prior to January, 1969. The incidence of breakage was higher for epicardial electrodes, but the main precipitating factor is the presence of acute angulation and areas of strain. Every effort is made to avoid any angulation of the electrodes during the procedure. Once a break occurs, especially if pacing has been lost, the patient should be explored and the whole electrode catheter should be replaced. Conversion to unipolar pacing proved effective in early cases and is still used occasionally. Repair of broken wires has not been practical or effective in our hands. Improvement in quality of the wires may also account for the lower incidence of breakage in recent years.

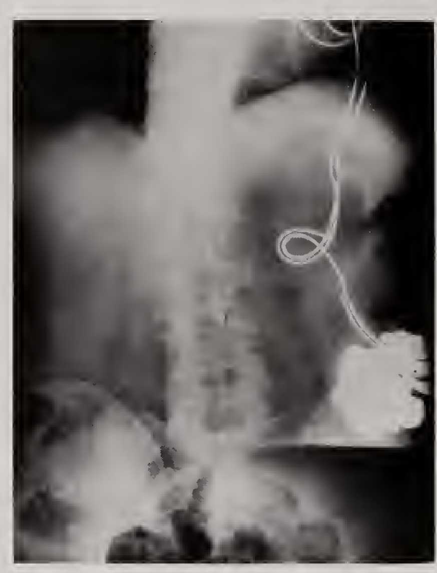


FIG. 3: Wire breakage resulting from direct blunt trauma to the area. Patient tried to push his automobile stalled in the snow and fell against the bumper with direct hit of the electrode area.

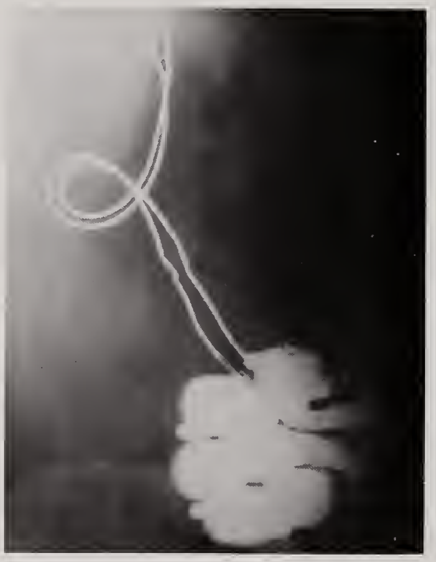


FIG. 4: Fracture of wire of electrode catheter which occurred spontaneously several months after original pacemaker implantation.

One of the most disturbing and annoying late complications is wound dehiscence at the pulse generator pocket and extrusion of the unit (Fig. 5). It occurred six times in our series, always several months after insertion (range two to six months). Exterioriz tion of the pulse generator and use c a specially tailored shoulder sling t support the unit outside the bod proved to be a good compromis procedure, in order to avoid reoper tion in two very old, weak patient Both are doing well 14 and 21 month later (Figs. 6 and 7). In one patient w successfully closed the wound se ondarily after temporarily removin the unit and gas-sterilizing it. In th other three patients a new pocket ha to be made in a different location.

Two patients developed late infe tion three and five months afte implantation. Both showed signs o septicemia which subsided after removal of the whole pacemaker system

There was one case of thrombosis o the subclavian and axillary veins 1 weeks after implantation.

In two instances we were unable t remove initially an endocardial catheter which had curled on itself. Constant traction with a one-pound weight for three hours was effective in one o those cases.

In three patients failure of the components was manifested by an increased rate (runaway pacemaker). All had fixed-rate models. One patient died as a result of the malfunction of the pulse generator, that occurred 24 months after insertion. The EKG on that patient showed firing of the pacer at a rate of 250 to 300 times a minute. She developed ventricular fibrillation and expired soon after admission to the hospital. Two other patients with runaway pacemakers survived after emergency replacement of their pulse generators.

The most common complication in the late postoperative period was premature failure of the energy supply. Almost 10% of all batteries failed during the first 18 months. Eighteen per cent failed during the next six months. Twelve percent failed between the 24th and 30th month. In other words, 40% of batteries failed before 30 months. With the demand

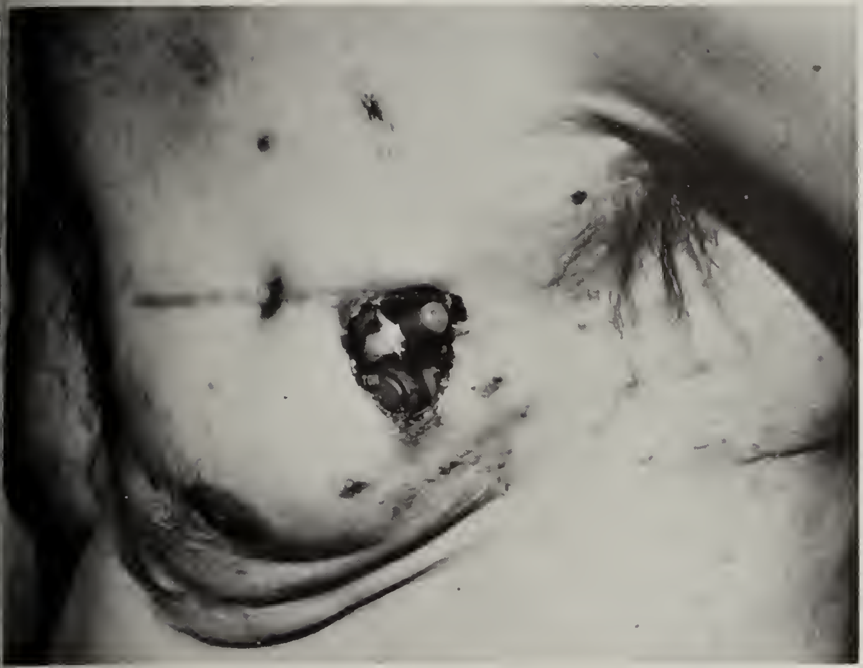


FIG. 5: Extrusion of pulse-generator in a 61-year-old, white male who had two previous replacements of his pulse-generator.

type of pulse generator, average battery life was 20.9 months; with the fixed-rate models it was 26.6 months. Consequently, we now advise patients with demand models to return more frequently for follow-up visits after 18 months and to anticipate elective replacement any time after 20 months. The manufacturer indicates that the new models (5842-5942, etc) will last longer, perhaps between 24 and 30 months.[11] Among those patients who refused to have elective replacement of their pulse generators, three continued to function well over 48 months. The longest one lasted 66 months.

Pulse generator failures were mostly manifested by gradual or intermittent drop of the pulse rate. Recurrence of cerebral ischemia symptoms occurred in 50% of the failures. None of our patients died as a result of premature pacemaker failure.

Mortality and Survival Rates

There were 13 deaths in the hospital among the 342 patients who received permanent units (3.8%). Among the patients receiving only transvenous electrodes, mortality was only 8 out of 312 (2.6%). Of those who underwent thoracotomy, five of thirty died (17%). The causes of death were pulmonary embolism (one patient), recent myocardial infarction (five patients), pulmonary edema and congestive heart failure (six patients), and ventricular fibrillation in the recovery room (one patient). The pacemaker was incriminated as a contributing factor in two of the deaths: one with ventricular fibrillation and one with pulmonary edema following a failure of pacing.

Survival rates of our patients who received permanent units are shown in Table 2. Late mortality due to malfunction of a pacemaker was documented in only one instance with a runaway fixed-rate pacer as mentioned previously.

Discussion

The enormous success of pacemakers tends to blind us regarding their failures. We still must strive to reduce the complications. Surgical morbidity is low. Hematomas and infections are infrequent. Perforations still occur but are not as dangerous as they sound.[4,12,13] Late dehiscence of the wound is a disturbing occurrence,[6] and it probably is directly related to the necessity for frequent replacement of the pulse generator. Conservative[14] management may be effective in many instances and should be attempted before replacement of the entire system. Although the bipolar endocardial electrode has given very satisfactory long-term results, its instability in the initial post-implantation period causes surgical readjustments to be necessary in a high percentage of patients.[15] Wire breakage is less frequent now than during the initial years, but still possible, even with direct trauma.[16]

The demand asynchronous type of pacemaker is most advantageous at present, because it requires only a simple procedure for implantation, and it has proven to be a very stable system for long term pacing with competitive rhythms almost completely eliminated. Synchronous pacemakers are more physiologic since they take advantage of the atrial contractions. The insertion of an atrial electrode, however, still presents a difficult problem. It may require thoracotomy or mediastinoscopy, since the transvenous insertion has not been adequately developed. Placement of two electrodes, atrial and ventricular, is even more uncertain at present, but it does have advantages for pa-

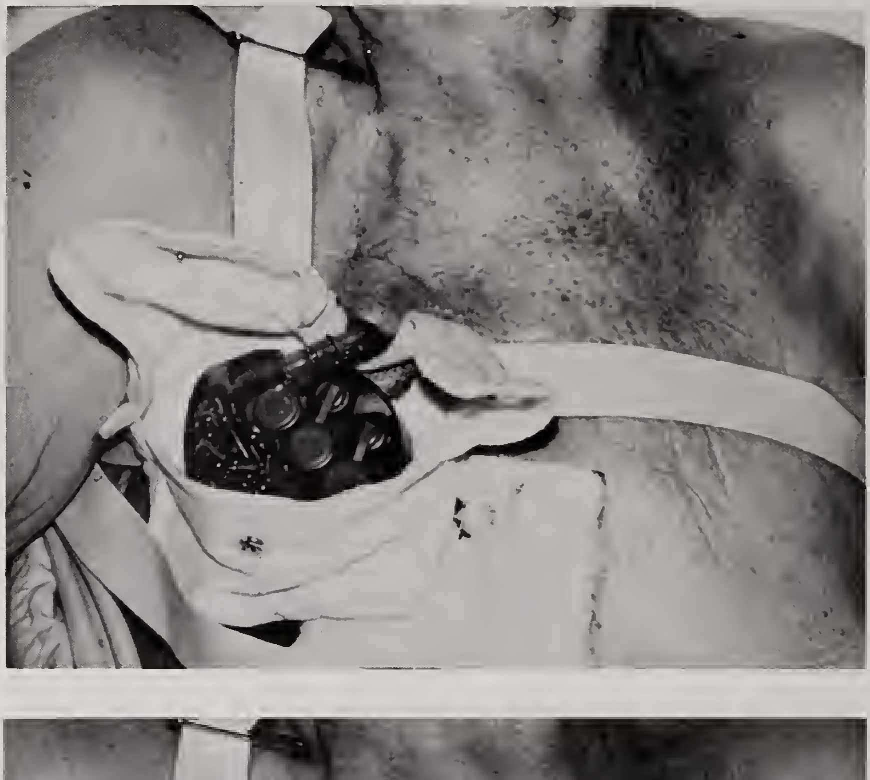
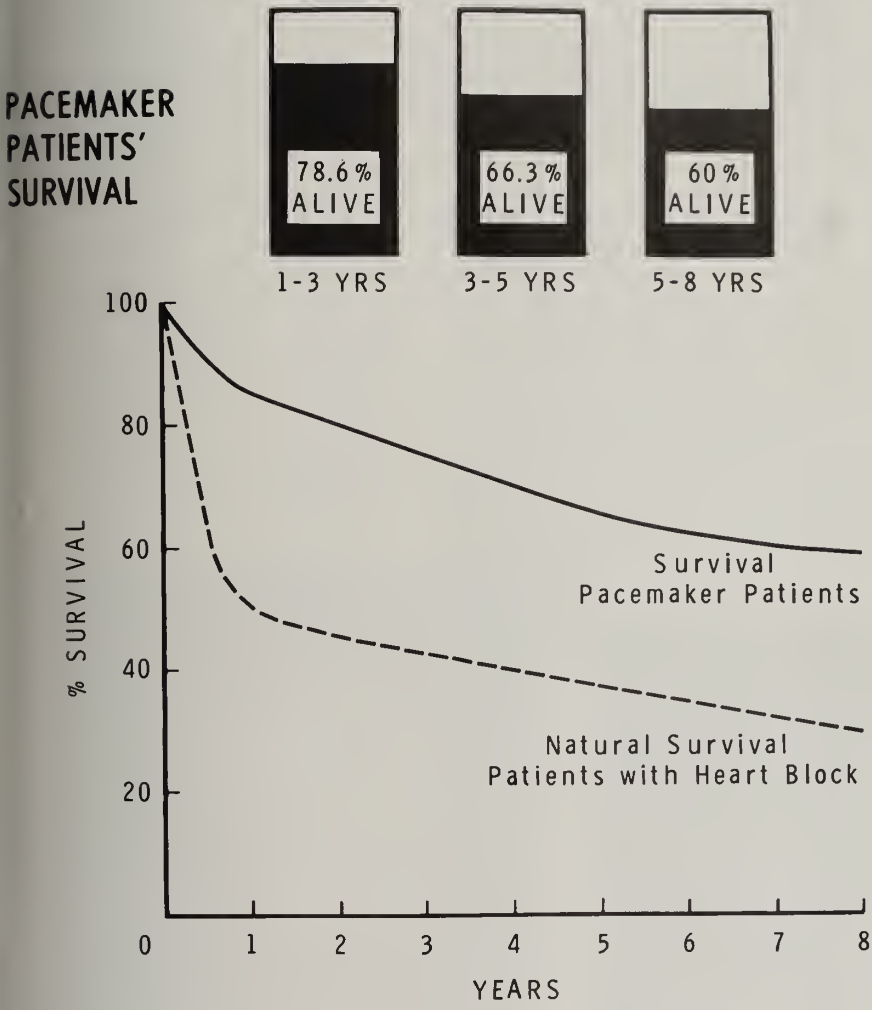


FIG. 6 & 7: Shoulder sling (open and covered) used for exteriorizing the extruded pulse-generators in very old and debilitated patients.

TABLE 2: Survival Rates Based on 181 Patients Who Received Permanent Cardiac Pacemakers Prior to 1971



tients with complete heart block and normal sinus rate function.

Partially implanted systems never have gained wide acceptance although they present real advantages. Since almost half of our patients cannot bother even to count their pulse daily as advised, it is doubtful that they would return for regular recharges of the units inside the body.

The present widely used pulse generator of the demand type has a shorter life than predicted.[17,18] Repeated replacements of pulse generators increase the likelihood of complications associated with incisions and wound healing. Devices and techniques for estimating the remaining energy in the pulse generator unit in order to predict the optimal time for elective replacement are not yet perfected.[18] There is hope that nuclear powered models will last much longer. Several atomic powered pacemakers have been implanted in Europe, mainly in France, and appear to be functioning well after 30 months.[19,20]

Tachyarrhythmias still take a high toll of lives of patients with healthy myocardium. We need drugs or devices to suppress this. A small number of patients with tachyarrhythmias can be helped indirectly by the insertion of standard demand pacemakers.

Summary

Our experience for over ten years with the use of cardiac pacemakers in 490 patients is presented with emphasis on the complications and their management. Most frequent complications were arrhythmias during the operative procedure, loss of electrode position in the early postoperative period, and premature exhaustion of the power supply in the late postoperative period. Other less frequently seen complications were difficulty establishing endocardial pacing, hematomas, infections, wound dehiscence, perforation of the right ventricle, diaphragmatic clonus, runaway pacers, and wire breakage.

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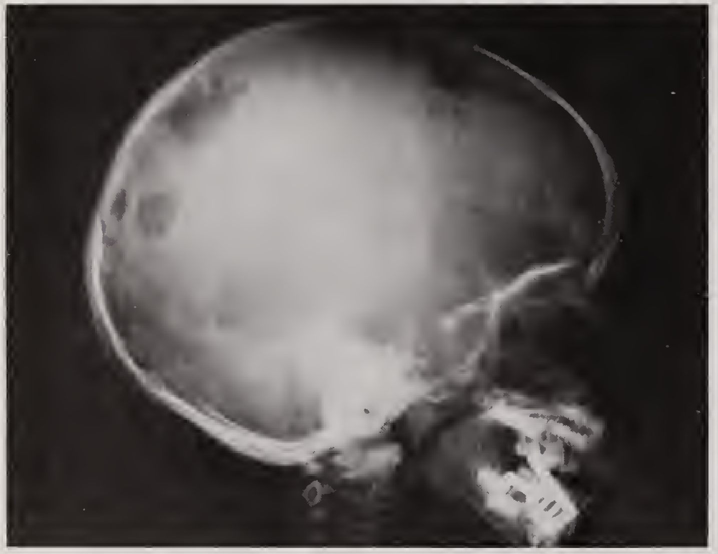
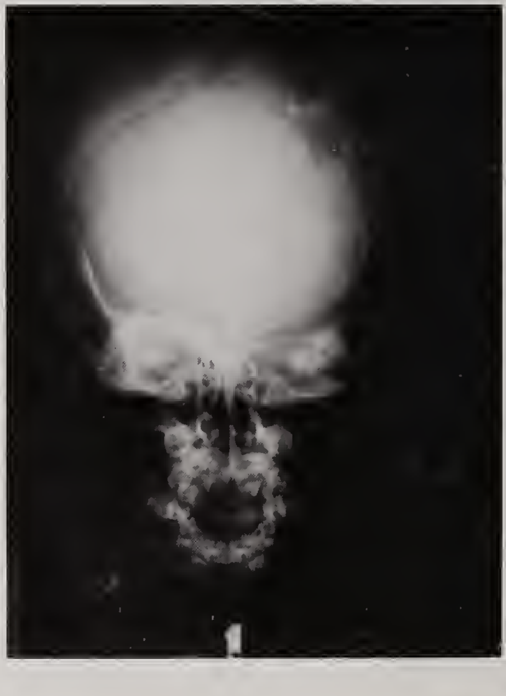
THE VIEW BOX

Prepared By
The Department of Radiology
Washington Hospital Center

A three year old girl presents with left-sided unilateral exopthalmos. There were no endocrine abnormalities or other significant findings on clinical examination.





(for diagnosis see page 184)

Pseudoaneurysm After Angiography*

STANLEY PERL, M.D., LOUIS WENER, M.D. AND WILLIAM S. LYONS, M.D.

Introduction

Pseudoaneurysm as a complication of percutaneous arteriography is well known. A pseudoaneurysm is a hematoma which develops following arterial puncture or spontaneous rupture of an artery with extravasation of blood into the tissue around the vessel. The opening in the vessel remains patent. Lang[1], surveying 300 angiographers, reported three instances in 11,402 procedures. Bergentz[2] et al reported 15 cases (14 femoral and one brachial) of pseudoaneurysm occurring in 15,000 to 20,000 punctures over a five year period. Seidenberg and Hurwitt[3] described five cases of false aneurysm in approximately 1500 arteriograms. This paper presents two more instances of pseudoaneurysm following percutaneous arterial puncture and a description of the angiographic findings in this angiographic complication.

Case Reports

PATIENT 1.–F. A. W., (MCMH #004322), a 29-year-old man was admitted to Morris Cafritz Memorial Hospital on June 27, 1971, for evalution of hypertension. He was first found to be hypertensive (160/100) in January 1971, and demonstrated left ventricular hypertrophy and ischemia on EKG. Laboratory data were not remarkable. The radiorenogram was within normal limits. Hypertensive intravenous pyelogram revealed symmetrical nephrographic phases with prompt and equal appearance of the contrast material bilaterally. The left kidney was 1.5 cm smaller than the right. Retrograde midstream aortography and selective renal arteriography were performed through a right femoral arterial puncture. These studies were normal except for a small cortical cyst in the upper pole of the right kidney. Renal vein renins, drawn through a left femoral vein puncture, revealed:

Inferior Vena Cava–1560 nanograms/100 ml plasma
Left Renal Vein–950 nanograms/100 ml plasma
Right Renal Vein–1295 nanograms/100 ml plasma

These values are in the range for malignant hypertension rather than unilateral renovascular hypertension. The arterial studies were accomplished without incident and no hematoma was detected at the puncture site following withdrawal of the catheter. The patient remained flat in bed until the next day when he was discharged on medication to control his hypertension.

Seven weeks later, the patient approached the angiographer and described a painless bulge which had appeared in his right groin within the past several days. Physical examination revealed a non-tender, 6 cm. mass in the right femoral area, which did not pulsate. Although a pseudoaneurysm was suspected, the presence of an undiagnosed pretibial skin lesion and a small inguinal draining pustule raised the question of an infected inguinal node. The patient was placed on antibiotic therapy and compresses to the groin for approximately one week and readmitted for evaluation.

A right femoral arteriogram was performed through a left femoral arterial puncture, demonstrating the hole in the right femoral artery and the pseudoaneurysm (Fig 1A and 1B). At surgery, the aneurysm was ruptured during dissection. A 2 mm perforation (Fig 2) in the anterior surface of the superficial femoral artery was found and closed with 4-0 arterial silk mattress sutures. The patient made an uneventful recovery and has experienced no complications from the second arterial puncture.

PATIENT 2.– A. R. S. (MCMH #166650), a 64-year-old woman was discharged from another hospital after evaluation of severe hypertension which included percutaneous femoral arteriography approximately nine days prior to admission at Morris Cafritz Memorial Hospital. She stated no abnormalities were present at the puncture site at the time of discharge. A few days later she noted swelling in the right groin, which developed into a tense painful lesion. The right lower extremity was slightly swollen and peripheral pulses were good.

The patient refused further angiographic study and was operated 24 hours after admission. A poorly developed pseudoaneurysm (a large amount of clotted blood) was encountered and

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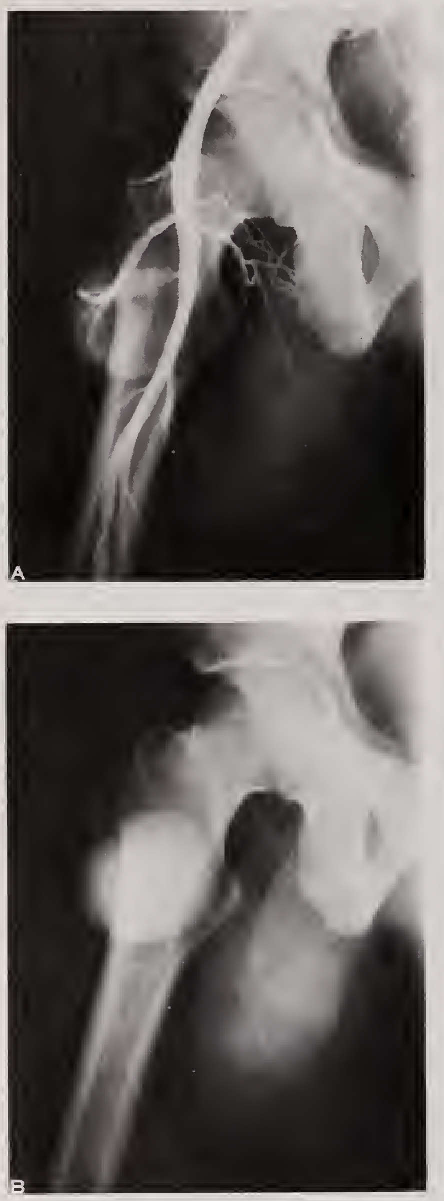

FIG. 1A. Right posterior oblique projection 1.5 seconds after injection: Note jet of contrast material from anterior surface of superficial femoral artery with filling of pseudoaneurysm. 1B. Seven seconds after injection: Persistent opacification of the pseudoaneurysm is noted.

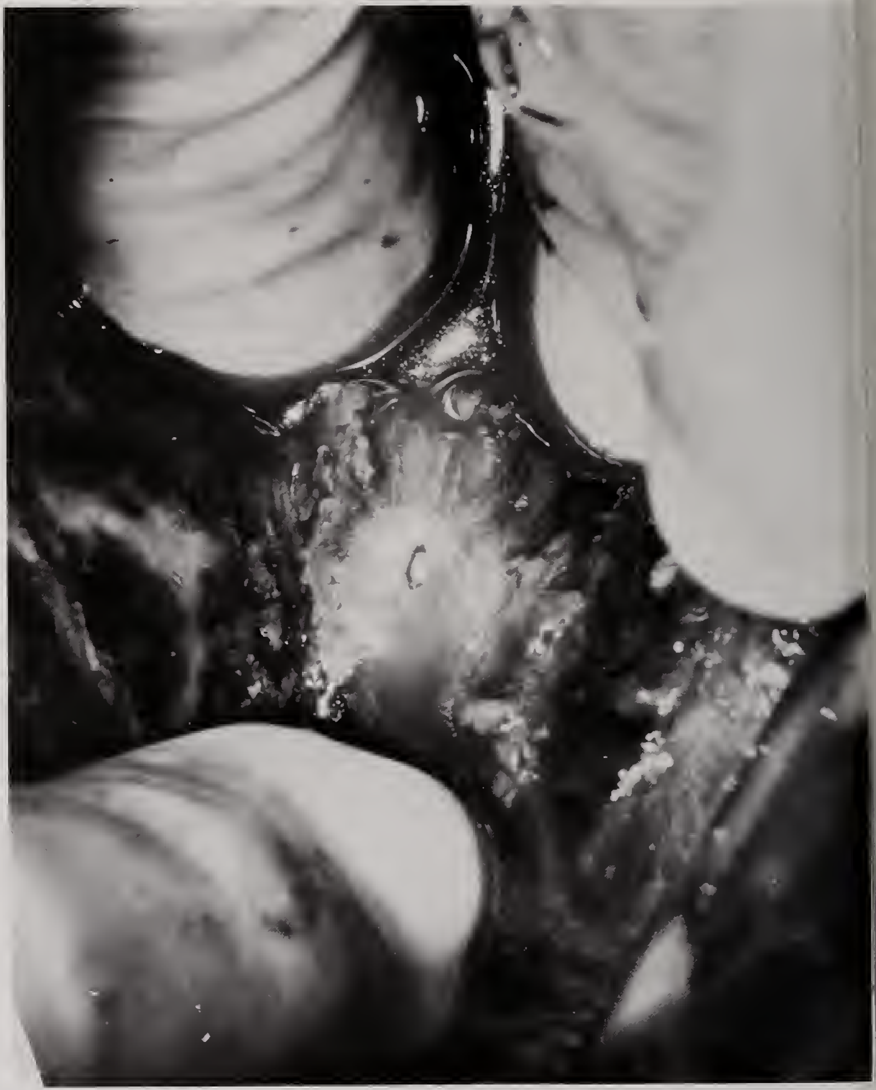

FIG. 2. Two millimeter hole in anterior wall of superficial femoral artery demonstrated at surgery.

removed. This was followed by brisk hemorrhage from a hole in the femoral artery, which was controlled by finger pressure while two 5-0 silk sutures were placed. No further bleeding was encountered and the wound was closed. The post-operative course was uneventful.

Discussion

The apparent incidence of pseudoaneurysm as a complication of all arterial punctures is 0.07%. Two predisposing factors which have been suggested on hypertension and inadequate compression of the femoral artery following the puncture. The appearance of a mass in the inguinal region following an arteriogram is typical. The mass may or may not pulsate, is usually slightly tender and is well demarcated. The lesion begins as a hematoma with extravasation of blood into the surrounding tissues. This clotted blood becomes the wall of the pseudoaneurysm as bleeding continues into the area. It takes two to six weeks for the lesion to completely develop. Surgical excision of the pseudoaneurysm and repair of the artery, either by primary suture of the hole or patch grafting, should be performed as soon as the diagnosis is made, for the pseudoaneurysm may rupture with recurrent bleeding and pain. Interestingly enough, the only two deaths reported in the Seidenberg and the Bergentz papers occurred in patients operated upon for pseudoaneurysm, one from rupture of a mycotic aneurysm of the abdominal aorta and the other from a post-operative cerebral hemorrhage.

Summary

This is the first published arteriographic demonstration of a pseudoaneurysm at the site of the percutaneous femoral arterial puncture. Predisposing factors are mentioned. It would appear that extra care should be taken to assure hemostasis at the arterial puncture site in hypertensive patients.

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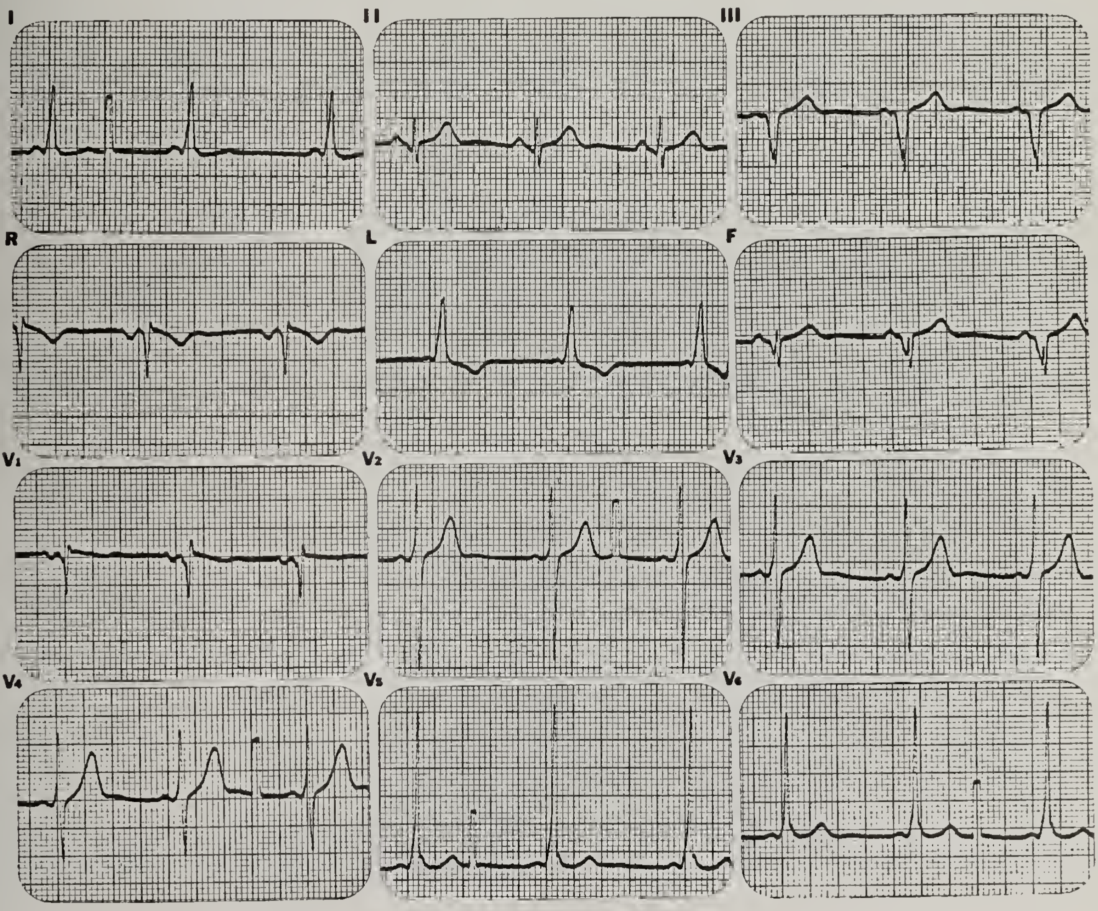
ECG Problems

HISTORY: 25-year-old, Caucasian male referred because of rejection for life insurance. Cause of rejection was the electrocardiogram.



(for diagnosis see page 188)

Postoperative Abdominal Wall Necrosis

CHARLES M. AARONSON, M.D.*

Introduction

A rare and frightening complication of abdominal surgery is a peculiar progressive, superficially gangrenous process designated by Meleney[1] as synergistic or symbiotic bacterial gangrene. This appears generally within ten days of abdominal surgery, especially following procedures involving a suppurative appendix or other intra-abdominal infection. Initially there is bright erythema surrounding one of the sutures, but it promptly distinguishes itself from a banal bacterial suture infection by aggressively spreading centrifugally across the abdominal surface. As the well demarcated bright pink margin spreads outward, the central area takes on a cyanotic and then gangrenous hue, followed by sloughing. The central sloughing keeps pace with the outward progress of the margin, so that a distance of approximately 2–10 cm. separates margin from slough. Patients characteristically complain of exquisite tenderness at the advancing margin, but despite the terrifying speed with which the abdominal skin is destroyed, it is only the superficial skin and connective tissue which is lost[2], and islands of epithelium may remain within the ulcerated area[3]. The term "phagedena" has been applied to this process[4]. During the course of this ailment, the general condition of the patient remains good. Temperature elevation is usually minimal, and appetite and vital signs generally are satisfactory[5]. However, from a psychological viewpoint, patients display growing demoralization and depression at the inexorable advance of the slough. It has been postulated that the central necrosis and undermining of the skin are the result of a wave of destruction from the infection as it sweeps through the superficial capillaries and venules[6].

Because Meleney described other clinical forms of gangrene of the skin, it is important to draw a distinction between them. His original contribution on this subject concerned hemolytic streptococcal gangrene[7]. In this process one is chiefly concerned with lesions of the extremities which undergo rapid deep denuding skin necrosis, and the skin is so extensively undermined that a probe may be inserted an inch or more in any direction. The skin necrosis is associated with a highly toxic course: high fever and prostration are the rule. Multiple lesions affecting several areas are seen in reported cases, and the disease is not necessarily preceded by surgery. From an etiologic standpoint, hemolytic streptococci are the cause. This distinguishes it from postoperative synergistic gangrene, in which Meleney incriminated a symbiotic combination of hemolytic staphylococcus and nonhemolytic microaerophilic streptococci.

When these conditions were first studied, the treatment of choice was wide and complete excision of the active border[8]. In a subsequent report[9] Meleney updated therapy to include topical zinc peroxide paste, sulpha drugs and bacitracin. Even since the discovery of penicillin, excision of the entire active border in postoperative synergistic gangrene or in progressive postoperative abdominal wall necrosis may still be necessary, as recently reported by Alexander[10]. For practical purposes, it is often impossible to obtain accurate bacteriological information based on inocula from the enlarging ulcer because of the presence of antibiotics that were administered at the beginning of the process before the clinical picture had developed. Even when cultures are taken before initiating antibiotic treatment, microaerophilic streptococci are difficult to isolate and require reduced oxygen to grow out. It is not unusual to face a grim situation in which cultures are negative or unproductive, antibiotics are apparently ineffective, and the area of necrosis of the abdominal wall continues to enlarge. The following case report illustrates the clinical problem outlined, and the manner in which it was resolved may be helpful in the management of similar problems in the future.

Report of Case

The admission hemoglobin was 14 gm., hematocrit 42%, and white blood cells 16,200. Differential showed 89% segmented polymorphonuclears, 6% stab cells, 3% lymphocytes, and 2% monocytes. One day postoperatively the hemoglobin was 11.7 gm., hematocrit 36%. VDRL was nonreactive. Glucose was 88, blood urea nitrogen 8 mgm%, SGOT 37, LDH 125, total bilirubin 0.6 mgm%, cholesterol 214, uric acid 4.3, calcium 8.5, and phosphorus 4.5.

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On January 4, 1972, a 30-year-old full-term primigravida white married woman was admitted in labor to the obstetric service of Cafritz Hospital. After a period of nonproductive labor, due to cephalopelvic disporportion, fetal distress was detected and a caesarean section was performed. The mother received carbrital, meperidine, Phenergan, and scopalamine preoperatively; inhalation anesthesia was followed by intravenous methergine. The uterus, abdominal wall, and skin were closed in layers, the last with plain catgut.

Recovery seemed routine except for the onset of herpes zoster on the right midthoracic wall about the second or third postoperative day. Temperature elevation was 99.6 on January 5, 100.0 on the 7th, and 100.8 on the 8th, after which it remained in the area of 99.5 until a few days before discharge. The herpes zoster pain was controlled with Darvon. On the third postoperative day, January 8, a blister had formed over one skin suture and a bright red area had spread around the sutures. Ampicillin 500 mgm every six hours was started orally, while neosporin was applied as an ointment to the wound. Three days later, the area around the sutures had sloughed and a copious serous discharge was present with an undermined, well defined, highly tender peripheral border of bright pink.

Wound irrigations with peroxide and saline compresses were added, but by January 16 the entire suture line had sloughed. Cultures taken on January 13 had been negative. Local therapy was altered by substituting Burrows' compresses followed by topical chloromycetin, and tetracycline 250 mgm every six hours orally was substituted for Ampicillin. During the next four days the patient's abdominal skin continued to slough away superficially as the active bright pink zone moved outward to form an oval over the lower abdomen beneath the umbilicus. In the center of the oval lay shaggy red granulation tissue. The clinical appearance is shown in Figure 1.

During the course of this illness, the patient's general condition was good and her herpes zoster healed rapidly. Nevertheless, she became increasingly apprehensive about the abdominal ulceration and showed signs of depression with frequent crying spells. Careful attempts to aspirate material from the undermined border of the ulcer resulted in negative smears for bacteria, fungi, and protozoans, and cultures (aerobic, anaerobic, and for fungi) remained negative.

Her serum electrophoretic pattern was interpreted as "Nonspecific. Suggestive of acute infection or tissue necrosis." (Low albumin, elevated alpha one and alpha two globulins, with slight elevation of beta and normal gamma.) A skin biopsy showed "Dermis and fat . . . a dense infiltrate of polymorphonculear leukocytes, in some areas forming abscesses." On January 20, the patient insisted on going home to care for her baby, and was released to be followed daily as an outpatient. The author decided to approach the problem as a possible cytotoxic phenonemon related to inflammation and immunological factors rather than as a bacterial one alone, particularly since antibiotics had been ineffective and the patient was dubious about further surgery to excise the active margin of the ulcer. It was rationalized that wide excision of such a large area would be at least as incapacitating as the possible complications of systemic corticosteroids. Accordingly the patient began receiving 10 mgm of prednisolone every six hours, in addition to 250 mgm of tetracycline and topical chloromycetin application.

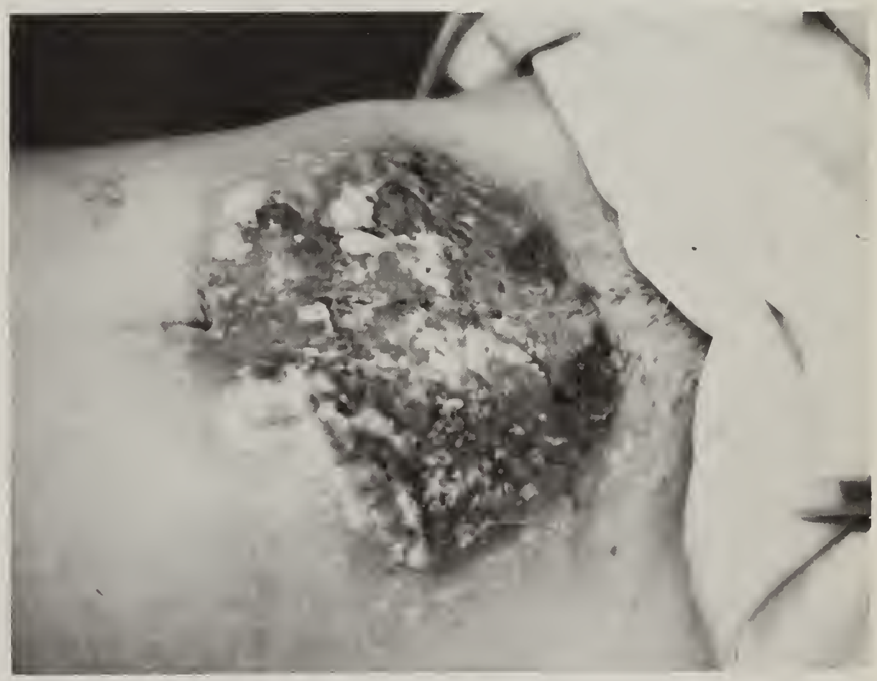

FIG. 1. Condition on January 20, 1972. White material is ointment. Note undermined border at top.

By January 22, the bright erythematous border had disappeared and the swelling at the ulcer margin had vanished with the undermining. Further ulcer spread halted simultaneously, and on January 28 the lesion had begun to epithelialize along the entire periphery and epithelial islands started to appear in the ulcer bed. The dose of prednisolone was halved. On February 3, a transient attack of urticaria required benadryl. The steroid was slowly tapered. On March 10, the ulcer was completely reepithelialized and all drugs had been stopped. The appearance at this time is seen in Figure 2. The only complication during this treatment was slight facial rounding. The baby was normal from the time of delivery and remained in good health.

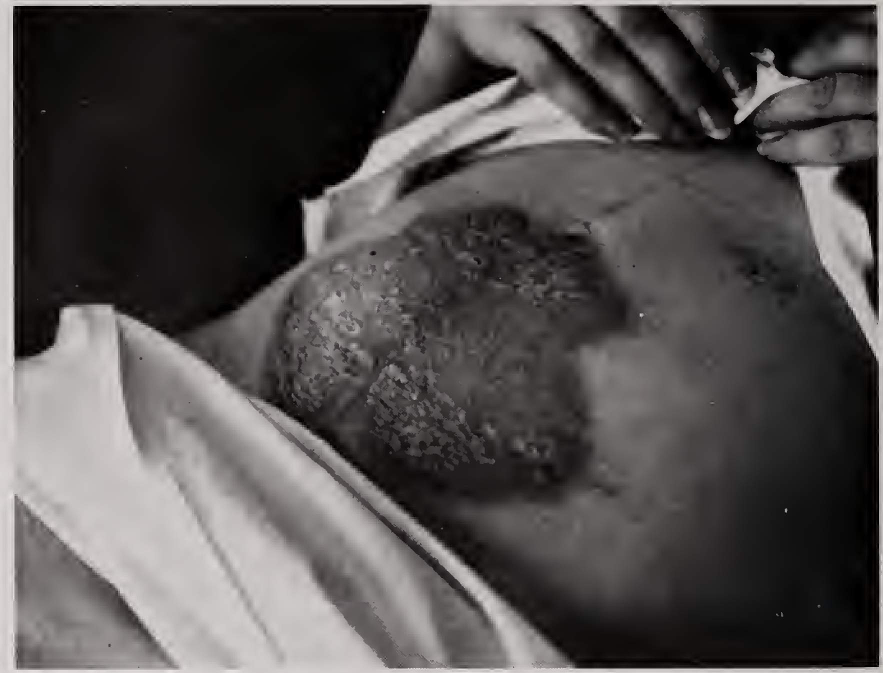

FIG. 2. Condition on March 10, 1972: hyperpigmentation and adherent crust of dried scale.

Discussion

The advent of penicillin and other antibiotics has taken much of the danger out of wound infection management, but progressive postoperative abdominal wall necrosis, or gangrene, is not necessarily responsive to antibiotics. It has been suggested even quite recently[10] that wide excision of the complete wound margin may be necessary to halt what has, on occasion[11], been a fatal disease. The failure of a clinical syndrome of postoperative abdominal wall necrosis to respond to penicillin or other antibiotics raises doubt that all cases of this syndrome are, in fact, explainable as a symbiosis between hemolytic staphylococcus and nonhemolytic microaerophilic streptococcus, as originally hypothesized by Meleney. For example, it was reported by Karn[12] that in one case in which penicillin and zinc peroxide had been ineffective, streptomycin in customary intramuscular dosage was promptly curative. Undoubtedly a variety of microorganisms in combination may play an etiologic role and some may be insensitive to most available antibiotics. Obviously it would be best to culture any postoperative wound infection before starting an antibiotic, but the point of greatest concern here is the refractory nature on occassion of postoperative abdominal wall necrosis to most antibiotics and the evident disadvantages of halting it via total excision of the active border using a cutting current electrode. Perhaps if practiced before the disease has affected a large area of skin debridement in this manner would be more acceptable, but in terms of cosmetic outcome it is less than ideal.

In the case under discussion, as an alternative to excision of the ulcer the patient received a course of systemic corticosteroid (prednisolone, ten milligrams every six hours, for approximately a week). The dramatic success of this relatively small dosage and its freedom from side effects, suggest that this may well serve as a rational alternative to wide ulcer resection in those cases where antibiotics are incapable of halting the disease.

Although Meleney felt that synergism of the hemolytic staphylococcus and nonhemolytic microaerophilic streptococcus accounted for the clinical syndrome of postoperative gangrene, subsequent experience has shown that other organisms may cause the same problem, and in the present case no microorganisms were ever isolated. This case may also be the first in which the disease was preceded by herpes zoster. Thus, we may be justified in conjecturing that not only combinations of bacteria, but also combinations of virus and bacteria could be involved. In fact, the remarkable degree of tissue necrosis, characterized by massive numbers of polymorphonculears clogging vessels and forming abscesses, is reminiscent of a non-allergic gangrenous process long familiar as an experimental model: the Shwartzman phenomenon. A number of human ailments characterized by unexplained necrosis, such as "phagedenic ulcer, pyoderma gangrenosum, lazarine leprosy, and necrotic reactions following the injection of living or dead bacterial or viral or bacterial filtrates" have been connected with the Shwartzman phenomenon in a speculative way[14]. It seems reasonable that postoperative necrosis of the abdominal wall may be a necrotic process due in part to a disturbance of the efferent limb of the immune system at the point of release of cytotoxic factors by the polymorphonuclear leukocytes. If so, then it is logical that corticosteroid therapy be a treatment of choice. Jannsen, *et. al.*, in a recently published textbook[14] have suggested systemic and locally injected corticosteroid therapy as an adjuvant to conventional management of this disease. It is noteworthy that corticosteroid treatment has been used frequently in pyoderma gangrenosum, an odd type of progressive superficial gangrene of the skin associated with ulcerative colitis. Here, however, the primary inflammatory cell found in the lesions is the lymphocyte.

Summary

A clinically typical case of postoperative bacterial synergistic gangrene (postoperative abdominal wall necrosis) has been reported. This may be a unique instance in which the ailment developed as a complication of caesarean section in full-term primigravida with concurrent herpes zoster. Failure of the rapidly progressive abdominal wall necrosis to respond to penicillin or tetracycline, with topical neosporin and chloromycetin, in the absence of demonstrable organisms in the lesion, necessitated a trial of prednisolone orally in moderate doses. This was promptly curative. The pathogenesis of postoperative abdominal wall necrosis as a nonspecific cell-mediated cytotoxic phenomenon in humans (Shwartzman-like) was discussed.

Acknowledgment

The author wishes to express his appreciation to Dr. Masud Homayouni for valuable assistance in preparation of this report.

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Primary Carcinoma of the Vagina
Case Report and Review of the Literature

ROBERT C. HECKER, M.D.*

Primary carcinoma of the vagina is one of the least common malignant tumors of the female genital tract, being second in rarity only to malignancy of the Fallopian tubes.[1]

According to Palumbo *et al,*[1] the incidence of vaginal carcinoma varies from one to four percent. Underwood and Smith[2] feel that this rarity may not be real, since in the past, the patients died from invasive carcinoma of the cervix before reaching the age when vaginal carcinoma is most common (50 to 70 years).

The criteria for the diagnosis of primary vaginal carcinoma as outlined by the International Federation of Gynecology and Obstetrics[3] are: a clinical origin in the vagina, an uninvolved cervix and no evidence of a metastatic etiology.

Report of Case

A 35-year-old white woman, gravida III, para III, was seen December 8, 1971 complaining of backache and soreness in the vagina of two months' duration. Past history included a D & C and cautery of the cervix in 1969 for "staining" of one month's duration. Diagnosis of dysfunctional uterine bleeding and retroverted uterus was made. Vaginal examination revealed a 3cm. granulomatous appearing lesion in the middle one-third of the posterior vaginal wall. The cervix was cystic with the uterus in 3° retroversion, normal size and shape. The Pap smear was reported as Class 1 and the chest x-ray was negative. Wide excision of the vaginal lesion was done under general anesthesia on an In & Out basis December 13, 1971. Histological examination revealed extensive squamous cell carcinoma in situ. Surgical margins of the specimen were clear. On December 20, 1971, a D & C and cold knife conization of the cervix were done. There was no evidence of malignancy in this material. After consultation with the radiotherapist and pathologist, we believed that we were dealing with a primary vaginal lesion of low grade malignancy with no invasion. The decision was made to treat with intravaginal radiation. A total dose of 8000 rads was given in divided doses approximately two weeks apart using a vaginal carrier containing 20 mgm Cesium at the apex, 15 mgm in the central and 15 mgm in the distal portion. Follow up pelvic, rectal, and cytological examinations were made periodically with no evidence of recurrent disease after one year.

Discussion

Herbst *et al*[4] from Massachusetts General Hospital listed the following symptoms in a total of 68 patients between 1927 and 1963:

1. Postmenopausal bleeding	42.7%
2. Post-coital bleeding	8.8%
3. Intermenstrual bleeding	10.3%
4. Spotting	5.9%
5. Discharge	10.3%
6. Pain	5.9%
7. Frequency, dysuria and others	16.1%

The Gynecological Tumor Registry at North Carolina Memorial Hospital, Chapel Hill, North Carolina has reported an additional 49 patients since Palumbo *et al*[1] reviewed 13 patients in 1953. The mean age was 55.7 years. Eleven patients were premenopausal, nine had surgical menopause and 29 were postmenopausal. Thirty of the 49 presented with either bleeding or watery discharge. Three patients noted a mass in the vagina. None reported pain.

Underwood and Smith[2] from the Medical University of South Carolina reported 35 cases (1.6% incidence) with 50% over age 60. Three patients were in their 20's. Their primary presenting symptom was abnormal bleeding in 50% of cases and 25% complained of unusual discharge.

All reports agree that the upper one-third of the vagina was the most common site of origin. Parity, marital status and race had no apparent relationship. Questionable etiological relationship to pessaries, weight pattern and procidentia was not supported by these series.[5,6]

Most lesions were grossly exophytic and classified as epidermoid carcinoma.[1,2,7] They were staged according to the International classification and were preponderantly found to be Stage II.[8] Staging of tumors is prognostically significant and useful for evaluating therapy.

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Factors that will govern therapy include the location of the lesion, age, the medical status of the patient, the necessity of maintaining a functioning vagina, the clinical stage and extent of lesion, and the high complication rate. The lymphatic drainage of the upper one-third of the vagina is similar to that of the cervix, with drainage to the pelvic nodes, while the lower one-third is primarily that of the vulva, going to the inguinal nodes. Therefore, the location of the lesion is extremely important. Also, tumors of the lower one-third of the vagina may involve the bladder and rectum.

The team approach with radiation therapist, pathologist and surgeon in addition to the tumor board recommendation is mandatory for careful planning and individualization of each patient.

Radiation therapy with Bloedorn applicators for lesions in the upper one-half of the vagina, and either Bloedorn or vaginal cylinder for mid-vaginal lesions is recommended for selected cases, but not for lower one-third lesions due to higher dosage required with resultant greater complications to the vestibule and hymenal area.[2] In this area, interstitial implants were recommended.[1,2] External radiotherapy may be used alone or in conjunction with radium or surgery. Individualization of modality is required, with a total dosage in the range of 5000 to 10,000 rads.[1,2]

Surgical treatment offers a choice of wide excision, simple vaginectomy, radical vulvectomy and groin dissection, and exenteration. These may be used in conjunction with irradiation in selected cases.[2,3,9]

Summary

Primary vaginal carcinoma (clinical origin in the vagina, an uninvolved cervix, no evidence of metastatic etiology) is a rare entity that occurs primarily in older women, without a known etiology. The most common symptoms are abnormal vaginal bleeding and an unusual discharge. Other complaints such as pain, vaginal mass, urinary frequency or dysuria are minimal. Some patients are asymptomatic, the lesion being seen on routine examination. This finding adds support to the recommendation for yearly pelvic examination and vaginal cytological screening, especially in post-hysterectomy patients.

Early diagnosis is necessary for effective therapy. It has been demonstrated that, the longer the duration of symptoms, the lower the survival rate. Herbst, *et al* state the "Vaginal carcinomas are external lesions and therefore more accessible to early diagnosis." [4]

The lesions of primary carcinoma of the vagina vary from 2 to 7+ centimeters, are most often exophytic or ulcerative and can be staged according to extent, with more than 80% of the cases being squamous cell carcinoma. These lesions can be seen by examining the entire vagina.

Considerations of therapy include age and medical status of the patient, location (origin), type, size and extent of the lesion. Individualization of the treatment is mandatory for management of primary carcinoma of the vagina.

Early diagnosis plus adequate surgery and/or radiation therapy should improve the results of treatment of this malignancy. Better radiation techniques and more aggressive management of irradiation modalities can lead to improved survival rates.

Studies are being pursued regarding the occurrence of primary vaginal carcinoma in young women whose mothers were given stilbestrol in pregnancy.

Acknowledgment

The author wishes to acknowledge the technical assistance of Mrs. Dell M. Strickler, R.N.

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Sporotrichosis of the Thumb. A Case Report

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Introduction

Sporotrichum Schenckii is a dimorphic fungus with worldwide distribution and may be recovered from soil, vegetation and animals. Most published cases involve those adults with exposure, in their occupation, to rose bushes, sphagnum moss and packing straw.

Report of Case

A 40 year old white female presented at the surgeon's office in mid-January, 1971 with a complaint of "something, probably a thorn, under my left thumb nail." She had been in Florida two weeks before and had worked in a garden which contained rose bushes, but did not remember what had stuck her. Examination showed some redness, and slight swelling of the skin at the edge of the left thumb nail, and a whitish linear deformity extending 2-3 mm. beneath the nail. At the first visit, a portion of the nail was cut away and the area probed unsuccessfully for a foreign body. There was no pus. She was instructed to use hot saline soaks and neo-sporin ointment dressings, and was given a tetanus toxoid booster (her last tetanus toxoid booster had been six months to a year earlier). She returned two days later, still complaining of pain, with extension at the area of redness around the edge of the nail to the lateral cuticle. One week after the first visit she noted a tender, hot, red streak up the forearm with elbow pain, and she was started on penicillin by injection and by mouth. An X-ray of the thumb was negative. One week later it appeared she had a typical paranychia and an incision and drainage was done. There was necrotic skin, but no actual pus. At this time more nail was removed and a tiny 2-3 mm. piece of "thorn" was found and removed. The lymphangitis was improved although it now appeared that she had some thrombotic nodular veins along the forearm. By February 3rd she had the onset of what appeared to be a furuncle of the base of the same thumb, on its dorsal aspect, and the oral penicillin was discontinued and tetracycline begun. She had no febrile reaction. A culture which had been done at the time of the I&D showed a light growth of a Candida species. A urinalysis was within normal limits, and a fasting blood sugar was 110 mg.%. The tip of the thumb had an unusual appearance, with much granulation tissue overgrowing the nail, but no actual suppuration. At this point, the possibility of sporotrichosis was raised after a discussion with the pathologist. The "furuncle" at the base of the thumb was incised and two cultures taken. The patient was then started on iodine soaks (PVP) and saturated solution of potassium iodide by mouth. An initial dose of 20 drops (1 ml.) orally t.i.d. was then increased daily by 0.5 cc. until 10 cc. were given daily. The SSKI was continued for approximately two weeks after the lesion had healed. One week after starting therapy the thumb looked better although she now complained of axillary tenderness on the left, but examination showed only very small, nontender lymph nodes in the axilla. Two weeks after treatment had begun she noted definite improvement in both the appearance of the thumb and the tender nodules of the forearm. Of interest is that the patient, who had had a previous subtotal thyroidectomy for multinodular thyroid disease, noted the presence of a nodule in the mid low anterior neck above the typical thyroid collar scar. This nodule was about 1 x 1½ cm. in size and moved on swallowing. At this point (February 17th) the thumb appeared perfectly normal except for the cutaway nail. By March 15th the nodules beneath the skin of the forearm had disappeared, as had the one at the base of the thumb which was incised for the cultures which produced (on March 4th) the elusive Sporotrichum. This was isolated after successive recultures and will be described later. The thyroid nodule has subsequently decreased in size and is no longer palpable.

Discussion

A recent editorial[1] discusses several outbreaks of lymphocutaneous Sporotrichosis, in unusual settings. The sources of infection were from bales of prairie hay in Kansas; from either soil, Spanish moss or packing straw used for storing bricks in Florida, with a third instance from rose bushes. Nine children[2] who had played in prairie hay in the midwest developed classical lymphocutaneous Sporotrichosis. Three had adjacent subcutaneous nodules but none developed secondary ulcers. All were treated with saturated solution of potassium iodide with complete healing in four to seven weeks. Outside the epidemic areas Sporotrichosis, because of its relative rarity, may prove to be a diagnostic enigma to clinicians who are not acquainted with the clinical picture of this mycotic infection, a chronic cutaneous (or rarely pulmonary and systemic) fungus infection caused by S. Schenckii. The disease was first recognized by Schenck in this country in 1898 and shortly afterward by Beurmann and Ramond in France. It has a world-wide distribution but most of the cases have been reported in the U.S.A. and France, although the condition is apparently common in Cuba among meat packers as an occupational disease. Sporotrichosis is probably one of the most common and serious systemic fungus diseases. The infection is usually of exogenous origin, the organism being transmitted to man from plants, especially barberry thorn. It is rarely transmitted from man to man but may be acquired from the bite of infected animals such as horse or rat.

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The disease begins as an indurated nodule, usually on the upper extremities, which eventually ulcerates and fails to heal. The hands are the primary site of infection in 37.5% of the cases; in 25% of the cases, the lesion first appears on the forearm, while the upper arms and legs are the primary site in 5% and 9% of the cases respectively. Spread of the infection occurs through the lymphatics, resulting in the appearance of multiple nodules along the course of the lymphatics which eventually ulcerate with draining sinuses. The spread usually stops at the regional lymph nodes, although it may rarely be systemic, with metastatic lesions involving the lungs, liver, and especially the testes. The systemic disease may be complicated by arthritis or rapidly progressing cutaneous infection resembling pyoderma gangrenosum. Occasionally the cutaneous lesion may be firm and resemble a syphilitic granuloma. Undoubtedly, at least some of the previously reported cases of syphilitic infections responding to iodide therapy represent instances of sporotrichosis. The tissue reaction is suppurative and granulomatous. The occurrence of partially acid fast asteroid bodies may prove helpful to the pathologist in suspecting the condition. The organism, a gram positive cigar-shaped budding yeast, is rarely found in the infected tissue of man. The availability of fluorescent antibody techniques, however, has proved very helpful. On the other hand, the organisms can be readily demonstrated in peritoneal exudate of the highly susceptible mouse injected intraperitoneally with the infected material. This results in widespread peritonitis and orchitis, and is a valuable aid in recovery and identification of sporotrichum schenckii.

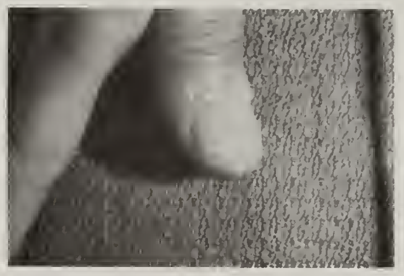

FIG. 1. Thumb during acute phase while under treatment with SSKI.

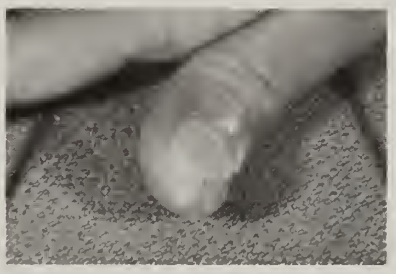

FIG. 2. Thumb toward end of treatment.

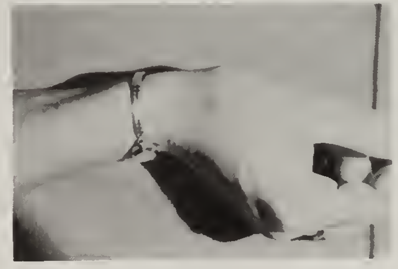

FIG. 3. Healing subcutaneous nodule at wrist and nodularity in forearm.

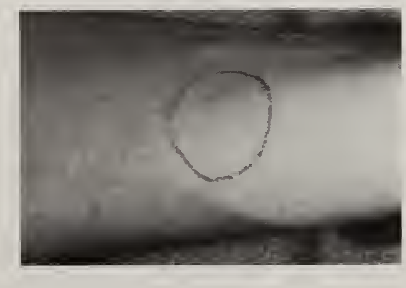

FIG. 4. Nodule of forearm.

In view of the paucity of the causative agents in the tissue, proper mycological examination and animal inoculation is mandatory for establishment of the diagnosis. *Sporotrichum schenckii* is a dimorphic organism. It has a yeast-like appearance when grown on enriched media, such as cystene agar at 37° C., but has a mold-like characteristics when grown at room temperature. Conversion of the mold phase to yeast phase is fairly difficult in vitro but can be readily achieved by intraperitoneal or intratesticular injection of rats or mice. On Sabourand's dextrose agar incubated at room temperature, the colonies appear in two to five days. The colonies are at first white and creamy but on continued incubation become dark brown. Microscopically, the mycelial phase shows delicate branching septate hyphae 1-2 microns in diameter. Oval conida are borne on lateral condiophores, often in flower shape arrangement.

Infection is followed by appearance of agglutinins and complement fixing antibodies. A skin test "sprotrichin" is available which may be of value in diagnosis.

Treatment of choice is KI by mouth. This therapeutic modality is quite specific but must be continued for several weeks after apparent healing of the lesion.

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THE VIEW BOX

(from page 172)

DIAGNOSIS: Histiocytosis X (reticuloendotheliosis)

Letterer-Siwe disease, Hand-Schuller-Christian syndrome and eosinophilic granuloma probably are different presentations of the same disease.

Histologically, there is a proliferation of reticulum cells in various organs. Often flat bones are involved, with skull and pelvis highest in frequency.

Radiographically, there are solitary or multiple lucencies with sharp borders. The lesions are scalloped in outline, irregular and without sclerotic borders. Often they are confluent and, in the skull, have a map-like or geographic appearance.

Note in this case the extensive involvement, especially of the left orbit, which led to exopthalmus.

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Azotemic Malignant Hypertension: Clinical Course and Survival With Vigorous Anti-hypertensive Regimen and Intermittent Dialysis*

ILUMINADO A. CRUZ, M.D., MARTIN G. DILLARD, M.D. AND ADRIAN O. HOSTEN, M.D.

Abstract

Twenty eight patients with malignant hypertension and severe renal failure were vigorously treated with antihypertensive agents and intermittent dialysis. Criteria for inclusion in the study were diastolic blood pressure of 130 mm Hg or higher, grade III or IV eyeground changes, and BUN of at least 50 mg.%. Headache was the most common presenting symptom, followed by symptoms of cardiac failure. Survival rate in one year was 33% and mean duration of illness was 7.8 months. In this study vigorous antihypertensive therapy assisted by intermittent dialysis did not significantly increase survival.

The term malignant hypertension was introduced in the literature by Volhard and Fahr[1] in 1914. Since then it has been well recognized that this syndrome has several causes of which malignant nephrosclerosis is one of the most frequent. This lesion was first described by Fahr, who emphasized the diffuse inflammatory changes in the renal arterioles. Published reports[2–8] of patient survival vary widely, but in general, survival depends on the severity of diastolic hypertension, the degree of renal insufficiency and the treatment instituted. The more recent studies[6,7] based on aggressive antihypertensive therapy with or without dialysis have claimed improved survival. However, we have been impressed by the severity of the hypertension and the almost invariably fatal outcome in our patients despite vigorous therapy. This report presents our experience with this disease.

Methods of Study

This was a retrospective study of patients with malignant hypertension seen at Freedmen's Hospital from July, 1968 to December, 1971. Criteria for inclusion in the study were the presence of diastolic blood pressure of 130 mm. Hg. or greater, at least grade III eyeground changes and blood urea nitrogen (BUN) of 50 mg.% or greater. Therapy consisted of either intravenous diazoxide, trimethaphan or apresoline, followed by various combinations of oral methyldopa, guanethidine and apresoline. In 24 cases, oral methyldopa or guanethidine was given doses increasing progressively to 4.0 gms. and 200 mg. respectively. In all patients, daily sodium intake was restricted to 34 meq/l or less. Furosemide was given intravenously to the oliguric anuric patients, and orally to those who responded, as well as to the non-oliguric patients who were in heart failure. All patients in heart failure also received digoxin. Where indicated, peritoneal or hemodialysis was instituted to control renal failure.

Results

A total of 28 patients met the criteria for study. There were 20 males and eight females. All were Black, nine were less than 30 years old, 14 were less than 40 years old, and only six patients were above the age of 50 years. The mean age was 40.6 years. Half of the patients had a past history of hypertension but 11 of the 14 patients under 40 years old, and seven of the nine patients under 30 years, had no previously known history of hypertension. Twenty one per cent had documented urinary tract infection in the past.

Headache, the most common presenting complaint, was seen in 72% of the cases. This was followed by symptoms of cardiac failure including dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and edema (57%). Twelve patients on admission had signs

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of congestive heart failure such as distended neck veins, ventricular diastolic gallop, cardiomegaly, and crepitant rales. Pericardial friction rub was present in 11 patients.

Of the 15 patients who received intravenous furosemide (up to 400 mg.) only four had a diuresis of 1000 cc. or more per 24 hours. Sixteen patients had adequate response in blood pressure, the diastolic pressure falling to 100 mm Hg or lower. Twelve patients were unresponsive or after initial transient response subsequently became resistant to antihypertensive medications. Twenty-six patients had repeated peritoneal dialysis, and four of them were subsequently placed on chronic hemodialysis using a twin coil artificial kidney. One of the four underwent bilateral nephrectomy with resulting normalization of his blood pressure. However, he died 11 days after surgery from septicemia and massive gastrointestinal bleeding.

Survival of our patients was very poor. Only nine patients were alive after one year. Four were still alive at 14, 15, 16, and 18 months respectively. Two are on chronic hemodialysis. The known duration of illness of those known dead varied from less than one month to 22 months, with a mean of seven months for the oliguric group and 10 months for the non-oliguric. The overall mean was 7.8 months.

Discussion

Malignant hypertension is generally rapidly progressive and leads to irreversible vascular damage and early death unless timely and aggressive treatment is instituted. The prognosis in untreated cases is very poor, the mortality being about 90% within a year of diagnosis (Table I). Medical treatment has improved prognosis to a limited extent. Harington et al[5] compared the results of 82 patients treated at Hammersmith Hospital with a control series of untreated cases from the same hospital. They found the life expectancy in the medically treated patients was six to eight times that of the control group.

Nonproprietary and Trade Names of Drugs
Furosemide–Lasix
Methyldopa–Aldomet
Guanethidine–Ismelin, Esimil
Trimetaphan–Arfonad
Digoxin–Davoxin, Digoxin, Lanoxin
Hydralazine–Apresoline

Survival of patients is significantly affected by the degree of renal insufficiency. Perry, et al[7] noted a one year survival rate of 84% for non-azotemic patients as compared to 54% for those whose non-protein nitrogen was over 30 mg.%. Woods and Blythe[6] had a 55% one year survival rate for their azotemic malignant hypertensives, who received vigorous antihypertensive therapy (Table I). Harington et al[5] reported a 73% one year survival rate for patients whose blood urea was below 60 mg.%, but only 13% for those whose blood urea was greater than 60 mg.%. No wonder Breckenridge[9] considered the initial blood urea as the single most important prognostic factor.

Since 1968, we have been combining dialysis with vigorous antihypertensive regimens in the management of patients with azotemic malignant hypertension. Despite large doses of potent antihypertensive drugs and efforts to keep the patients at their dry weight by salt restriction, diuretics and hypertonic dialysis, almost half of our patients had suboptimal blood pressure control. This has also been noted by other workers in some patients on maintenance dialysis. These patients had higher plasma renin activity than the responsive group, and their blood pressure was more easily controlled following bilateral nephrectomy.

There are several features about our cases which are worth emphasizing. As in the series reported by Kincaid-Smith[2], and by Heptinstall[4], there is a preponderance of males (70%). Also, while the mean age of our patients does not significantly differ from those series, it is noteworthy that 33% of our patients were less than 30 years old. Heptinstall reported a mean age of 38 years for his series of 41 predominantly white patients, but subsequently he was struck by the early

TABLE I: Survival Rates From Different Studies

Authors	No. of cases	Degree of Azotemia	Treated	Per cent One-Year Survival
1. Keith, et al[8] (1939)	146	–	No	21%
2. Schottstaedt & Sokolow[3] (1953)	104	–	No	12%
3. Kincaid-Smith, et al[2] (1958)	197	–	No	10%
4. Harington, et al[5] (1958)				
	45	Blood Urea < 60 mg%	Yes	73%
	37	Blood Urea 60 mg% or >	Yes	13%
5. Perry, et al[7] (1966)	97	NPN Normal	Yes	84%
	65	31 mg% or >	Yes	54%
6. Woods & Blythe[6] (1966)	20	BUN 50 mg% or >	Yes	55%
7. Our Group (1972)	28	BUN 50 mg% or >	Yes	33%

appearance of the disease in young Black patients[12].

While Schottstaedt and Sokolow[3] and Kincaid-Smith's group[2] reported a previous history of hypertension in 70%, 50% of our patients (including 11 of 14 patients below 40 years old, and seven of the nine patients below 30 years old) were admitted without any such history. This is especially significant because Breckenridge[9] recently claimed that the incidence of malignant hypertension has diminished and suggested that this was due to adequate treatment and follow-up of patients with essential hypertension, 1% to 8% of whom may develop malignant hypertension[13]. Admittedly, we cannot be certain about the negative history of hypertension, since many of our patients had not had previous medical examinations. The fact remains that malignant hypertension does arise de novo. We are convinced that this mode of presentation is fairly common among young Black males.

The most ominous development in the course of malignant hypertension is the spontaneous onset of oliguria or anuria. Muehrcke[14] reported six patients with acute oliguric renal failure due to malignant nephrosclerosis, all of whom died within 29 days of onset of oliguria. All of the four cases reported by Mattern, et al[15] died within three and one-half months despite hemodialysis. Three of the nine cases in the series of Linton, et al,[16] having as their underlying lesions chronic glomerulonephritis, eclampsia, and bilateral hydronephrosis secondary to bladder neck obstruction, were oliguric. Only the eclamptic survived. Sheer and Jones[17] described a case of malignant hypertension with severe oliguric renal failure arising in the postpartum period. She survived for a mere two months. Sevitt et al[18] reported ten cases of malignant hypertension, nine of whom had changes consistent with malignant nephrosclerosis, and all with severe oliguric renal failure. In all of them, antihypertensive therapy was coupled with peritoneal or hemodialysis. Six died within two months of onset of oliguria. Only one lived over one year. In our series, of the 15 oliguric patients, histologic sections were available in nine. Eight of these showed malignant nephrosclerosis, and one chronic pyelonephritis. Four survived less than three months, and four for more than a year. This was not significantly different from the survival of our non-oliguric patients, three of whom lived only two months, and five for 14 or more months. Thus, our experience seems to blur the significance of oliguria.

Possible factors in the pathogenesis of the initial oliguria include arteriolar narrowing resulting in ischemic tubular necrosis, heart failure, hypovolemia due to vomiting, and iatrogenic factors such as precipitous fall in blood pressure secondary to antihypertensive therapy and dialysis induced reduction in solute load. The specific histological lesion is probably less important, since oliguric renal failure in this setting is not unique to malignant nephrosclerosis.

On the other hand, Bonar et al[19] treated seven patients with intermittent peritoneal dialysis and three patients with intermittent peritoneal dialysis and three of them recovered from prolonged anuria. Kincaid-Smith et al[20] treated three patients with malignant hypertension and microangiopathic hemolytic anemia with anticoagulant and noted improvement in renal function in two. Eknoyan and Siegal[21], reported a 23-year-old female who recovered after 19 days of anuria and was alive after two and one half years.

It is evident from our study and other previous studies that malignant hypertension with severe renal failure has a poor outcome regardless of the underlying renal lesions. Many patients have oliguria, heart failure and microangiopathic hemolytic anemia. The severe hypertension is difficult to treat and in many cases responds not at all. Recent experience of others demonstrates that the renal failure is not always irreversible and that vigorous therapy should always be attempted. Where necessary this should include dialysis both to control uremia and to maintain dry weight. However, some patients do not respond despite this therapeutic approach. Bilateral nephrectomy seems to be their only hope. Indeed, according to Wilkinson et al[22] and Lazarus et al[23] early nephrectomy not only lowers operative morbidity and morality, but also facilitates adequate dialysis and rehabilitation of patients. The major reservation about early surgical intervention is that it dooms the patients who would respond to drug therapy to seemingly precipitous and complete dependence on dialysis.

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ECG Problems

(from page 175)

INTERPRETATION: Wolff-Parkinson-White syndrome.

Note PR interval of 0.10 to 0.11 seconds, and QRS interval 0.08 to 0.09 seconds. The most significant abnormality is the slurring of the initial portion of the QRS complex. This is particularly evident in leads I, III, aVF, but also visible in the other leads. This is the "delta wave," the characteristic alteration of the QRS complex in this conduction aberration. The initial downward deflection in leads III and aVF is caused by a delta wave and does not represent a Q wave of old infarction as the first insurance examiner had supposed.

Edited by Robert R. Montgomery M.D.

Are Women's Fashions Necessary?

Reflections Following a Visit to the People's Republic of China

W. MONTAGUE COBB, M.D.*

> *Is not the life more than meat,*
> *and the body than raiment?*
> Matt., 6:25

Our visit to the People's Republic of China was a tremendous experience. Though our group was within its borders but 15 days, it will take a long time to digest fully all seen and heard. The PRC dates from 1949, the year of the Communist ascension to power. In a scant 23 years the miracle of the ages has been performed. China is the most populous country in the world with a population of over 850 million. It represents the oldest continuing civilization on earth, with a recorded history going back about 5,000 years. It has been a site of human habitation since pre-historic times, as Peking man, *Sinanthropus pekinensis,* lived there 500,000 years ago.

Throughout this long period, this vast country, with variable borders, has been accustomed to massive bloodshed somewhere in the realm. The most recent occurred during the Japanese occupation from 1937 to 1942, during which the Japanese acknowledge that 25 million Chinese lost their lives, while the Chinese claim the figure was 35 million. Even the Communist takeover involved much slaughter.

Today, however, there is peace in the land, albeit military presence is everywhere, as "eternal vigilance is the price of liberty." But the periodic famines, pestilences and floods, which regularly took thousands of lives in the past, are no more. This alone is surpassing achievement.

Infectious diseases, except for schistosomiasis in some regions, have been practically eliminated. Universal cleanliness is a way of life. Cities, villages and countryside are free of litter and of rats. Narcotic traffic has been destroyed. Venereal disease has been stamped out. Prostitutes have been "reeducated." Alcoholism is not a problem, nor is mental health. The single psychiatric hospital visited had only about 100 beds and was but half full, mostly of schizophrenics. The teachings of Chairman Mao Tse-tung are used, apparently effectively, for mental therapy. There is no unemployment or vandalism and the people, who throng everywhere, are friendly and do not look unhappy. One sees neither obesity nor malnutrition.

In our area of special interest as physicians, the achievements of the Chinese in their health care delivery system both in promise and performance appeared to exceed ours, but they constantly stress that they have made only a beginning and invite criticisms of anything they are doing.

Their practices involve a blending of traditional and western medicine. Their recent accomplishments in the use of the ancient procedure of acupuncture, specifically for anesthesia since 1958, have received world-wide attention. Their contributions to the therapy of burns and reimplantation of severed parts have been made available through scientific media.

Everything has a political focus. Today the peasant in the most remote province has been made to feel that he is important to the country and that the country has a concern for him. If he loses a finger in an accident, he believes that Chairman Mao wants him and the severed part, in a refrigerated box, flown to the nearest facility equipped and staffed for replantations. This has tremendous morale-building impact. The spirit of the old hymn has been imparted.

I sing because I'm happy,
I sing because I'm free,
For if He marks the sparrow's fall,
I know He cares for me.

Sex discrimination has been abolished. Men and women are political and legal equals. Before the "revolution" women had hardly the status of serfs. Now everywhere men and women are seen working together as administrators, executives, practitioners, diggers of ditches, pushers of wheelbarrows, etc. Men and women even dress alike, and thereby hangs our present tale.

Everyone wears the simple Mao coat and trousers, generally of dark color.

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* Dr. Cobb was one of a ten member delegation from the National Medical Association which visited the People's Republic of China, October 13-27, 1972.

On the ladies pants the zipper seemed to be on the side, but this is insignificant for our theme. Gradually it began to occur to the writer that here, but here, may be something momentous, for the uniformity of dress of men and women had deprived the ladies of none of their natural charm or femininity. One could give full time and attention to their faces and personalities without the distraction of what they were wearing. Is this not good?

The writer recalled how many times the gracious lady who has deigned to share his name nigh 44 years has said words to the effect of, "you don't pay any attention to what I have on." And he has had to reply, "No dear, because though you always look good to me, I see only your face and on your face your eyes, for is it not written that the eye is the light of the body and the window of the soul." What more can there be?

This, of course, is a limited personal attitude, but in China it is expressed in the life style of a whole people. Hence the question slowly arises, "Are women's fashions really necessary?" Think of the billions we expend annually on new garments just because of change of style, discarding old that are hardly worn. How many marriages that end in divorce because of wifely extravagance might be saved? Vanity of vanities, all is vanity!

But one may not pursue this inquiry lightly, for to what extent would the economy of our country be disrupted if changing fashions for women, and lately for men, were discontinued. How much unemployment would be produced if the fashion designers, clothing manufacturers, promoters of fashion shows, fashion magazine and society news and media writers would have to find something else to do? Also, what would become of all those employed in the cosmetic, perfume, jewelry and hair dressing industries? And so on.

And what about individual freedom? The writer shudders to recall the cold fury aroused from a financial cross section of women some years ago when at a party a press report that a famous lady spent $40,000 a year on clothes was being discussed. The reaction from his simple remark that no woman needs to spend that much on clothes made him tremble.

This is in no way a simple matter. Consider that man, *Homo sapiens* that is, is the only species in which nature's obvious intent to make the male the more attractive of the species has been reversed. Take the barnyard fowl, for example, where gorgeously plumed chanticleer, shaking comb and wattles, struts magnificently before his drably feathered hens who modestly follow at a respectful distance. Or the male gorilla, of about 460 pounds as he majestically leads his family through the forest, turning his great crested head this way and that to make sure that the way is safe. Even with man, natures' intent is clear. He is larger, stronger and decorated with a resplendent hair pattern which in full expression presents a bald pate and full mustache and beard, glorious to behold. But the ladies have turned this around so that the more infantile smooth skin, less rugged bony contours and mammary appendages must be ever more esteemed.

At each step our inquiry deepens in complexity, for this reverse female dominance is nothing new. There is the famous paleolithic figurine, the so-called Venus of Willendorf, found in Austria. This is of a nude female with generalized obesity and enormous breasts, suggesting a physical type common at that time. But this figurine is stylized and not an attempt at photographic representation. The arresting feature of present interest is her coiffure, which shows rolls of a planned design. Could it be that the hairdresser had made appearance in paleolithic times even before clothing?

Obviously, in the matter of women's fashions we deal with a question of such magnitude that no one could presume determining expertise. Certainly not this writer. But the values of our culture are certainly illuminated by its consideration. For the writer's own part it is still true that "the life is more than meat and the body than raiment." Although he dreads being caught by his wife for window-shopping, he delights, with Socrates, in walking through the market place, because it reminds him of so many things he doesn't need.

> *And why take ye thought for raiment? Consider the lilies of the field, how they grow? they toil not, neither do they spin: And yet I say unto you, That even Solomon in all his glory was not arrayed like one of these.*

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book REVIEWS

Essentials of Roentgen Interpretation, 3rd Edition. LESTER W. PAUL, M.D. AND JOHN H. JUHL, M.D. Price, $35.00. Pp. 1,144 with illustrations. Hagerstown, Maryland: Harper and Row, 1972.

There are a number of very basic texts in roentgenology and many detailed multi-volume, multi-author reference works. The purpose of this book, so state the authors Dr. Paul and Dr. Juhl, in the preface to the 1st edition, 1958, is to bridge the gap between the elementary text and the multivolume reference work. This is being accomplished in clear and concise fashion. The 3rd edition is brought up-to-date in context and literature reference. Many chapters have been rewritten or have been added. More emphasis is placed on angiography since this modality plays an ever increasing part in diagnosis and treatment of various conditions.

There are separate chapters on the osseous system, the brain and spinal cord, abdomen and gastrointestinal tract, the urinary and female genital tract, the chest, and finally, a chapter on disease of the face, mouth and jaws.

Literature references at the end of each chapter are up-to-date and kept within sensible limits. Most of the listed sources should be available in the average hospital and department library.

The reproductions of roentgenograms are not always first rate but are adequate to illustrate diagnostic points. The captions are precise.

This book should continue to be useful to medical students as introduction to the multifacetted aspect of diagnostic radiology and to the practitioners of any medical speciality in which Radiology plays a role. It will continue to be found, not on the shelves in many X-ray Departments, thick with dust, but on reading desks often used for fast and accurate reference.

GUNTER J. AUGUSTIN, M.D.

The Making of a Psychiatrist. DAVID S. VISCOTT, M.D. Price, $8.95. Pp. 410. New York: Arbor House, 1972.

Even though "The Making of a Psychiatrist" is a Book-of-the-Month Club Main Selection, usually a sign of considerable merit, I approached it with some reservations largely as a result of having read two mostly unfavorable reviews, but also because the title seemed somewhat imitative and faintly redolent of hack work. I am happy to report that in my opinion the book is a success on at least three levels: first, as a description of the actual events which occur in the residency training of a psychiatrist, second, as a personal account of an individual's reaction to his experiences, and third, as a discussion of the philosophical aspects of the treatment of psychiatric patients.

Dr. Viscott's approach to his material is chronological. He starts with the beginning of his residency on the psychiatric ward of a private general hospital and describes his rotation through the outpatient department, then on to the various wards, chronic and acute, of a state institution. He also served in the course of his training at penal facilities, working with both adults and juveniles. The last chapters of the book deal with the problems encountered in private practice. In all, a comprehensive survey is given of the types of psychiatry practiced today on an inpatient and outpatient basis.

Contrary to one of the criticisms offered of his book, Dr. Viscott is hardly a true believer. At one point or another, if he is to be credited, he must have proved quite a trial to his immediate superiors. Anyone who has ever sought psychiatric help and been disappointed, may find his doctor among Viscott's rogues' gallery: the administrator who cares more about procedure than the good of his patient, the analyst who is so uncommunicative that it is hard to tell whether he is awake or asleep, the practitioner who resorts to electroshock as a matter of course; they are all here and more.

Over the course of his training, Dr. Viscott appears to have developed a philosophy of treatment which works a good deal of the time, at least for him. It may be described as Direct Therapy, and consists of a generous amount of inter-personal involvement. He also believes in leveling with the patient. As an example, he says, "Whenever someone uses a lot of psychological jargon around you, it is a sign of two possible dangers: first they may be afraid of getting close to you and dealing with you as a human being with real feelings, or second, they may be trying to impress you. You don't need a mental health professional like that, although

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Precautions: The enzyme's optimal pH range is 7 to 8. Lower pH conditions have a definite adverse effect on the enzyme's activity, and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene and heavy metal ions such as mercury and silver which are used in some antiseptics. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before Santyl Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's solution do not interfere with the activity of the enzyme.

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin.

A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by protecting the healthy skin with a material such as Lassar's paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although none has been observed to date.

Adverse Reactions: Adverse reactions to Collagenase have not been noted when used as directed.

Dosage & Administration: Santyl Ointment should be applied once daily (or once every other day in the case of outpatients) in the following manner.

(1) Prior to application the lesions should be gently cleansed with a gauze pad saturated in normal saline, buffer (pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.

(2) Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odor, it is desirable to use an appropriate topical antibacterial agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with Santyl Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of Santyl Ointment. Should the infection not respond, therapy with Santyl Ointment should be discontinued until remission of the infection.

(3) Santyl Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds, or, when dealing with shallow wounds, to a sterile gauze pad which is then applied to wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

(4) Crosshatching thick eschar with a #11 blade is helpful. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

(5) All excess ointment should be removed each time dressing is changed.

(6) Use of the ointment should be terminated when sufficient debridement of necrotic tissue has taken place.

Overdose: Action of the enzyme may be stopped, should this be desired, by the application of Burow's solution U.S.P. (pH 3.6-4.4) to the lesion.

How Supplied: Santyl Ointment contains 250 units of Collagenase enzyme per gram of white petrolatum U.S.P. The potency assay of Collagenase is based on the digestion of undenatured collagen (from bovine Achilles tendon) at pH 7.2 and 37° C. for 24 hours. The number of peptides cleaved are measured by reaction with ninhydrin. Peptides released by a trypsin digestion control are subtracted. One net Collagenase unit will solubilize ninhydrin reactive material equivalent to 4 micromoles of Leucine.

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Varma A O et al: *Surg. Gynec. Obstet.* *136*:281, Feb. 1973.

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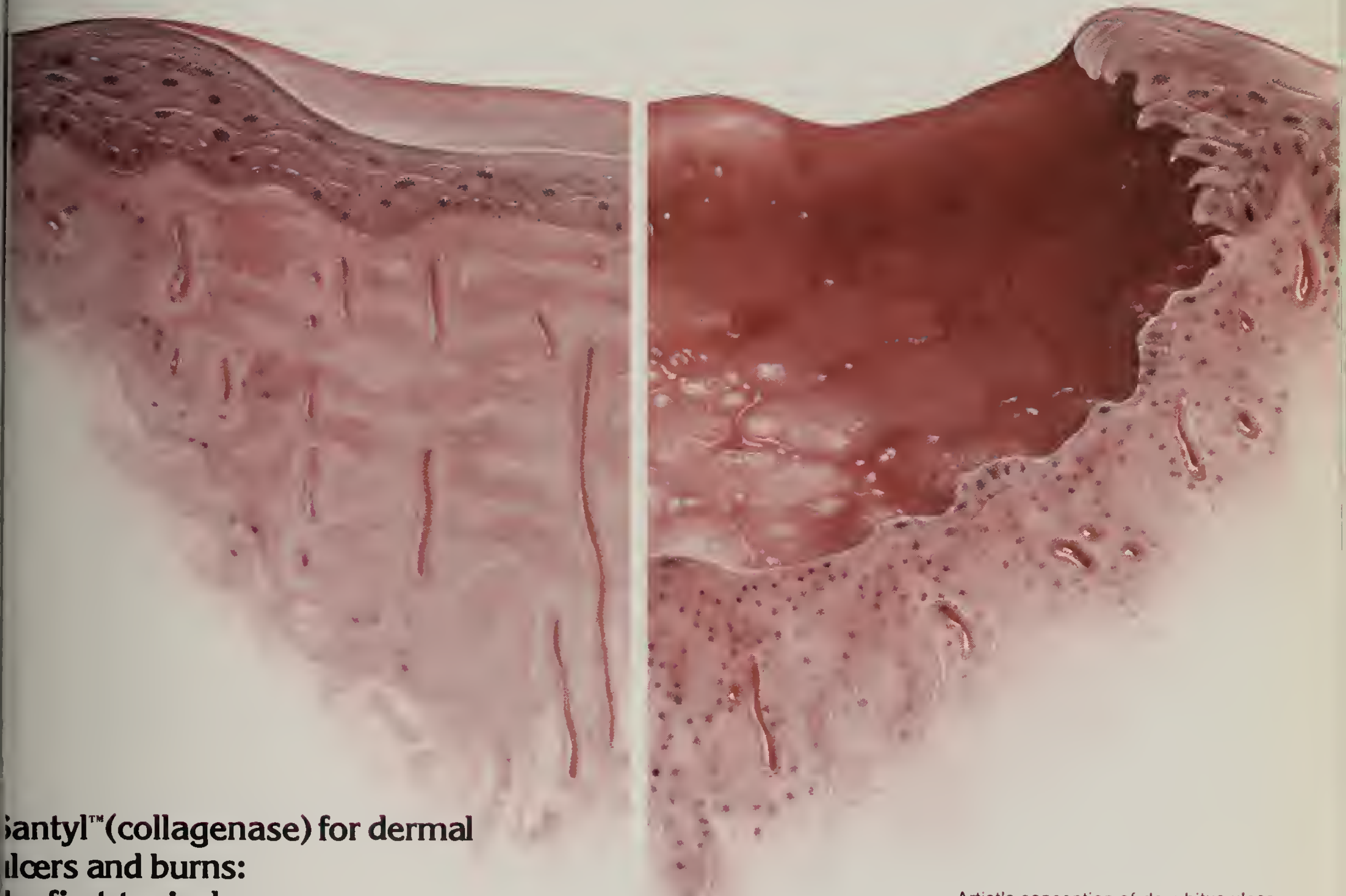

Artist's conception of decubitus ulcer

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to dissolve
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that's the kind that impresses committees and school boards and often gets hired because they sound good."

Analysts may feel that Dr. Viscott is overly critical of their methods. Certainly he is an opinionated person, one might even say, cocky, a characteristic he seems to recognize in himself. However, this book does not pretend to be an impartial survey, but rather the honest personal account of one man's experiences and feelings. As such, I think it is very valuable for the physician, in general, in that it sheds light upon a branch of medicine that is to many people mysterious and forbidding.

ROBERT E. MORAN, Jr., M.D.

Differential Diagnosis. The Interpretation of Clinical Evidence. A. MCGEHEE HARVEY, M.D. AND JAMES BORDLEY, III, M.D. Price, $12.00. Pp. 740. Philadelphia: W. B. Saunders, 1972.

The First Edition of "Differential Diagnosis" (1955) came to my attention in 1958. It consisted of 90 cases which had served as clinicopathological conferences at Johns Hopkins Hospital. Preference was given to clinical studies of the preceding 10 years to include the latest diagnostic procedures. Older cases were included so as not to deprive the reader of interesting and unique material. The book was unique and was recommended as auxiliary reading to yearly classes in Physical Diagnosis.

The Second Edition (1970) was much larger and more costly because of expansion of the general discussions and a great increase in the number of illustrative cases. While the expansion made the book more valuable as a reference it became more of a library text rather than a book for carrying by medical students.

The present abridgement of the Second Edition returns to the handy size and relatively low cost of the First Edition. The abridgement was accomplished with little sacrifice in value for the medical student. Some cases have been eliminated, the size of the printed page was reduced and thinner paper was used.

The book is highly recommended for students in Physical Diagnosis who wish to go beyond the basic textbooks, as well as all other medical students, interns and residents.

LAWRENCE E. PUTNAM, M.D.

Dermal Pathology. JAMES H. GRAHAM, M.D., WAINE C. JOHNSON, M.D. AND ELSON B. HELWIG, M.D., Editors. Price, $45.00. Pp. 1,155 with illustrations. Hagerstown, Maryland: Harper & Row, 1972.

When I was a resident and studied under Dr. Helwig ten years ago, he and Drs. Graham and Johnson had already made numerous contributions in the field of dermal pathology that were not to be found in standard works. Some of us asked Dr. Helwig at that time why he didn't write a textbook of his own. With characteristic modesty, he demurred. I am happy to say that he has changed his mind, because the book, "Dermal Pathology" is outstanding.

As with many texts, this one is a compilation of the work of many authors, edited by Drs. Graham, Johnson and Helwig. Although there are a few instances where different authors use different terminology, this sort of problem is kept to a minimum. Most of the contributors to the volume are recognized authorities who have published numerous times on their particular facet of dermal pathology.

The text begins with chapters on the normal histology and ultrastructure of the skin. The introduction continues with pointers on obtaining a biopsy, as well as a chapter by Mr. Lee Luna, the Chief of the Histopathology Division of AFIP, regarding the proper processing of skin biopsy tissue.

The bulk of the volume is devoted to the presentation of dermal pathology. In each section, clinical as well as pathologic descriptions are given. This should be of great help to the pathologist who is not as familiar with the gross or clinical appearance. There are many exceptionally clear photographs throughout the text and generally both low and high magnification views of each disorder are presented.

The chapters which deal with infectious processes are among the best I have seen anywhere. Descriptions of material not often biopsied, such as tinea capitis and dermatophytosis are presented in beautiful detail. The high light of the text to me is the description of the tumors of the skin, particularly the adnexal tumors. To me, Dr. Helwig and his associates have done their finest work in describing and categorizing the various sweat gland tumors.

There are some areas of the text which appear to be incomplete. The chapter on bullous dermatoses covers the subepidermal bullae in great detail, but pemphigus and the acute eczematous processes are neglected. Ichthyosis and many of the congenital disorders are similarly ignored. These criticisms aside, however, the text is clearly written, well illustrated and generally excellent. It should prove invaluable both to dermatologists and pathologists.

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The Human Spine in Health and Disease. GEORGE SCHMORL AND HERBERT JUNGHANNS, Translated by E. F. Besemann, M.D. Price, $38.00. Pp. 504, with illustrations. New York: Grune & Stratton, 1971.

Over the course of four decades, Schmorl's treatise on vertebral pathology has been published in five German and two American editions under the stewardship of H. Junghanns. The original work was based on a monumental post-mortem examination of more than 4000 spines. The structural analysis was both anatomical and radiological. This new edition has been revised extensively and the number of pages almost doubled. The illustrations and pathological core are faithful to the original. The expansion of the text represents largely an updating of pathogenetic mechanisms as deduced from clinical experience. There is an extensive bibliography and, for readers who do not understand German, a separate addendum of English-language references is provided. The quality of the illustrations again is high and the double-colume format is easy on the eye. The translation is completely new and competent. Some differences between German and American terminology persist; it will undoubtedly cause a moment's pause for Americans to know, for example, what is meant by vertebral chondrosis or osteochondrosis.

There are, despite the broad scope of its contents, some important gaps in the material covered. This stems, perhaps, from the fact that the original specimen material was derived from the thoracolumbar rather than the cervical portions of the vertebral column. It is disappointing thus to find no consideration of important entities such as rheumatoid arthritis or congenital narrowness of the cervical canal. As previously, the new edition is not primarily a clinical radiological text. It remains, however, an invaluable source of anatomical information for radiologists, pathologists and those concerned with clinical management of vertebral diseases.

LEON SOKOLOFF, M.D.
National Institutes of Health

The Genetic, Metabolic and Developmental Aspects of Mental Retardation. ROBERT F. MURRAY, JR., M.D., M.S., F.A.C.P. AND

PRESCRIBING INFORMATION

Antiminth (pyrantel pamoate) Oral Suspension

Actions. Antiminth (pyrantel pamoate) has demonstrated anthelmintic activity against *Enterobius vermicularis* (pinworm) and *Ascaris lumbricoides* (roundworm). The anthelmintic action is probably due to the neuromuscular blocking property of the drug.

Antiminth is partially absorbed after an oral dose. Plasma levels of unchanged drug are low. Peak levels (0.05-0.13μg/ml.) are reached in 1-3 hours. Quantities greater than 50% of administered drug are excreted in feces as the unchanged form, whereas only 7% or less of the dose is found in urine as the unchanged form of the drug and its metabolites.

Indications. For the treatment of ascariasis (roundworm infection) and enterobiasis (pinworm infection).

Warnings. *Usage in Pregnancy:* Reproduction studies have been performed in animals and there was no evidence of propensity for harm to the fetus. The relevance to the human is not known.

There is no experience in pregnant women who have received this drug.

Precautions. Minor transient elevations of SGOT have occurred in a small percentage of patients. Therefore, this drug should be used with caution in patients with pre-existing liver dysfunction.

Adverse Reactions. The most frequently encountered adverse reactions are related to the gastrointestinal system.

Gastrointestinal and hepatic reactions: anorexia, nausea, vomiting, gastralgia, abdominal cramps, diarrhea and tenesmus, transient elevation of SGOT.

CNS reactions: headache, dizziness, drowsiness, and insomnia. Skin reactions: rashes.

Dosage and Administration. *Children and Adults:* Antiminth Oral Suspension (50 mg. of pyrantel base/ml.) should be administered in a single dose of 11 mg. of pyrantel base per kg. of body weight (or 5 mg./lb.); maximum total dose 1 gram. This corresponds to a simplified dosage regimen of 1 cc. of Antiminth per 10 lb. of body weight. (One teaspoonful = 5 cc.)

Antiminth (pyrantel pamoate) Oral Suspension may be administered without regard to ingestion of food or time of day; and purging is not necessary prior to, during, or after therapy. It may be taken with milk or fruit juices. Because of limited data on repeated doses, no recommendations can be made.

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*Data on file at Roerig.

Please see prescribing information on facing page.

PEARL LOCKHART ROSSER, M.D., F.A.A.P., Editors. Price, $16.75. Pp. 343 with illustrations. Springfield, Illinois: Charles C. Thomas, 1972.

In 1969, the Howard University College of Medicine held a seminar on the genetic, metabolic and developmental aspects of mental retardation. This book is a collection of the papers presented at the seminar, though all the manuscripts have been updated and revised for this edition.

Part one contains 11 chapters concerning the correlations of mental retardation to human chromosomal aberrations, biochemical features, and molecular defects. The clinical syndromes, such as Down's, the aminoacidopathies, and the mucopolysaccharidoses are well covered. The chapter on the mucopolysaccharidoses is particularly well written. Generally, the chapters are short, succinct and informative, with excellent illustrations, graphs, and references. To those whose usual milieu is not the research laboratory, these chapters should be particularly enlightening.

Part two contains 14 chapters, which are more philosophical in outlook, generally longer, but, nevertheless, stimulating. These chapters cover mental retardation with its connection to perinatal influences, to the effect of class and the milieu, and to the problems of education. These aspects of mental retardation should be necessary reading for the clinically oriented, the physician, nurse, and biochemist.

The foreward states the purpose of this book, that it " . . . be of interest and value to all persons who play a role in the professional care of children both average and exceptional." This has been admirably done.

EUGENE J. CHAP, M.D.

Essentials of Cardiac Arrhythmias. Diagnosis and Management. SAMUEL BELLET, M.D. Price, $15.50. Pp. 458, with illustrations. Philadelphia: W. B. Saunders, 1972.

This text, published posthumously, represents a distillation of a much larger work. A great deal of the material was taken from the third edition of the author's book "Clinical Disorders of the Heart Beat". This latter, now classic text, is an enclylopedic coverage of arrhythmias constituting 1,317 pages as compared with the 458 in the volume under discussion.

The avowed purpose of this book is to supply a short, concise presentation on the subject of cardiac arrhythmias, and in this approach lies both its strength and weakness. Its great strength is the clarity and brevity with which the information is imparted; its unavoidable weakness, that of the superficiality with which it is of necessity treated. This is well recognized by the author in his introduction, and he concludes each chapter with an appropriate bibliography guiding the student to a more exhaustive coverage.

During the past decade there has been a resurgence of interest in cardiac arrhythmias, and a more sophisticated electrophysiologic approach to these problems. The text, while retaining a conventional approach to the subject, is exceptionally current in its treatment of more recent clinical advances.

The chapters on the common arrhythmias are lucid, well written and illustrated. One recognizes that he is reading the product of long thought by a dedicated educator. Some complex and uncommon arrhythmias are beyond the scope of this volume and not covered.

The therapeutic aspect of arrhythmias in coronary heart disease and myocardial infarction probably deserves a more extensive discussion in a book of this type than it is given.

His Bundle electrocardiography, and the diagnostic uses of rapid atrial pacing have excellent coverage, and the section on the pre-excitation syndromes is one of the best summaries I have seen. Coverage of stress testing and ambulatory monitoring is disappointing, but recognizable in view of the very recent nature of this material.

This book is highly recommended for those who are desirous of obtaining a lucid introduction, or overview to cardiac arrhythmias. It is one of the most readable texts I have ever gone through. It is as the author has indicated, aimed at interns, residents, medical students, intensive care unit personnel, and internists exposed to cardiac problems. It is insufficient information to use for therapeutic reference in many cases, but if the reader is prepared to search further for data from medical literature or his colleagues, it can be a first-rate framework on which to build.

ALAN M. WEINTRAUB, M.D.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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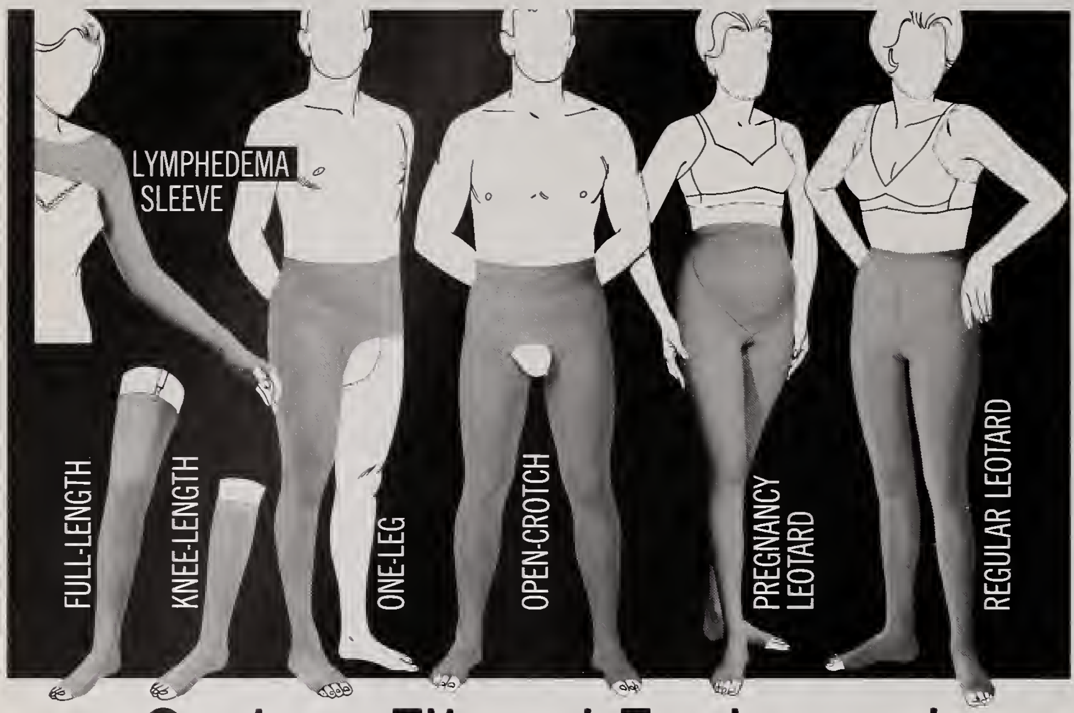
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obituaries

Kenneth F. Laughlin, M.D.
1913–1972

Dr. Kenneth F. Laughlin, a general practitioner in Silver Spring, Maryland for many years, died December 31, 1972. He resided at 1000 McCeney Avenue, Burnt Mills Hills, Silver Spring, Maryland.

Born in Crittenden, New York, he received a B.S. degree from Canisius College in Buffalo, New York, and his M.D. degree from Georgetown University School of Medicine here. He served both his internship and residency at Buffalo City Hospital, as well as a residency in pediatrics at the old Gallinger Municipal Hospital here. He was a clinical instructor in pediatrics at Georgetown University School of Medicine before entering the private practice of general medicine in Silver Spring, Maryland in 1938. He had also been on the staffs of the Washington Sanitarium and Hospital, the Washington Hospital Center, and Suburban and Children's hospitals.

An Associate member of the Medical Society of the District of Columbia for more than 30 years, Dr. Laughlin was also a member of the American Academy of General Practice, the American Medical Association, the Montgomery County Medical Society, the New York State Medical Society, and the Medical and Chirurgical Society of Maryland.

He is survived by six children, Kenneth Francis Jr., Daniel Jerome, Deborrah Ann, James Francis and Laura Jane, all of the home, and Kathleen Laughlin Campagnolo, of Newport, Rhode Island; six brothers and sisters, Vincent J., of Buffalo, John and Cyril, of Colesville, Maryland, Roland, of New York, New York, June Kerr of Woodcliff Lake, New Jersey, and Mary Klindworth, of Staten Island, New York; and one grandchild.

Thomas A. Gonder, M.D.
1912–1973

Dr. Thomas A. Gonder, a Washington area physician, died January 6, 1973. He resided at 314 South 2nd Street, Oakland, Maryland.

A native of Oakland, Maryland, Dr. Gonder received his B.S. and M.D. degrees from Duke University. He served an internship in medicine at Johns Hopkins Hospital and a rotating internship at West Baltimore General Hospital. He was a Fellow in Medicine at Johns Hopkins Hospital and had also done postgraduate work at the National Hospital for Nervous Diseases in London.

During World War II he served in three Central European campaigns as a medical unit commander in the U.S. Army. He held the rank of lieutenant colonel and was awarded the Bronze Star.

He had practiced Internal Medicine in Washington, D.C. and McLean, Virginia for 24 years and had been an associate professor of internal medicine at George Washington University School of Medicine. He moved his practice to Oakland, Maryland in 1971.

Dr. Gonder was a Special member of the Medical Society of the District of Columbia.

He is survived by his mother, Ann West Gonder, of Oakland; a brother, Richard, of Norfolk, Virginia, and a sister, Martha, of Sykesville, Maryland.

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Action: CANDEPTIN Vaginal Ointment, Vaginal Tablets, and VAGELETTES Vaginal Capsules possess anti-monilial activity.
Indications: Vaginitis due to Candida albicans and other Candida species.
Contraindications: Contraindicated for patients known to be sensitive to any of its components. During pregnancy manual Tablet or VAGELETTES Capsule insertion may be preferred since the use of the ointment applicator or tablet inserter may be contraindicated.
Caution: During treatment it is recommended that the patient refrain from sexual intercourse or the husband wear a condom to avoid re-infection.
Adverse Reaction: Clinical reports of sensitization or temporary irritation with CANDEPTIN Vaginal Ointment, Vaginal Tablets or VAGELETTES Vaginal Capsules have been extremely rare.
Dosage: One vaginal applicatorful of CANDEPTIN Ointment or one Vaginal Tablet or one VAGELETTES Vaginal Capsule is inserted high in the vagina twice a day, in the morning and at bedtime, for 14 days. Treatment may be repeated if symptoms persist or reappear.
Available Dosage Forms: CANDEPTIN Vaginal Ointment is supplied in 75 gm. tubes with applicator (14-day regimen requires 2 tubes). CANDEPTIN Vaginal Tablets are packaged in boxes of 28, in foil with inserter—enough for a full course of treatment. CANDEPTIN VAGELETTES Vaginal Capsules are packaged in boxes of 14 (14-day regimen requires 2 boxes.)

Store under refrigeration to insure full potency.

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References: **1.** Olsen, J.R.: Journal-Lancet *85* 287 (July) 1965. **2.** Giorlando, S.W.: Ob/Gyn Dig. *13*:32 (Sept.) 1971. **3.** Decker, A.. Case Reports on File, Medical Department, Julius Schmid. **4.** Giorlando, S.W., Torres, J.F., and Muscillo, G.: Am. J. Obst. & Gynec. *90*: 370 (Oct. 1) 1964. **5.** Lechevalier, H.: Antibiotics Annual 1959-1960. New York, Antibiotica Inc., 1960. pp. 614-618. **6.** Friedel, H.J.: Maryland M.J., *15*:36 (Feb.) 1966.

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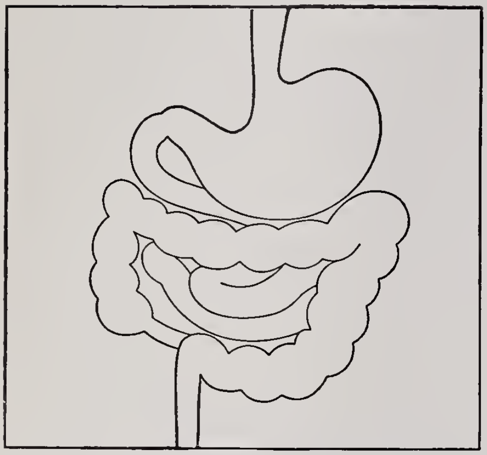
in "Gasspastic" conditions



The GI tract in spasm is commonly a "gas trap."

Sidonna® is formulated to release entrapped gas, as well as to provide antispasmodic/sedative effects.

In addition to the traditional combination of belladonna alkaloids and butabarbital (warning: may be habit forming.), Sidonna contains simethicone—a non-systemic defoaming agent that "lyses" gas bubbles on contact.

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Each scored tablet contains: Specially activated simethicone 25 mg.; hyoscyamine sulfate 0.1037 mg., atropine sulfate 0.0194 mg., hyoscine hydrobromide 0.0065 mg. (equivalent to belladonna alkaloids [as bases] 0.1049 mg.) and butabarbital sodium N.F. 16 mg. (Warning: May be habit forming.)

can do more

Contraindications: Anticholinergics should not be used in patients with glaucoma, known prostatic hypertrophy, or pyloric obstruction. Urinary retention may indicate the presence of prostatic hypertrophy. If it occurs, the dose should be reduced or the drug withdrawn. Also contraindicated in patients with known hypersensitivity to one of the components.
Side Effects: Dryness of the mouth, blurred vision, dysuria, skin rash, constipation or drowsiness may occur.

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McNEIL McNeil Laboratories, Inc., Fort Washington, Pa. 19034

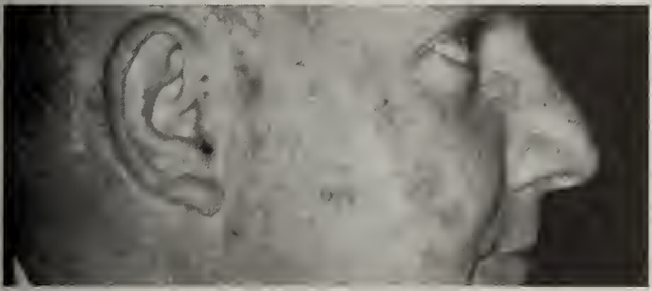
What's on your patient's face...

may be more important than
his chief complaint

The lesions on his face may be solar/actinic—so-called "senile" keratoses...and they may be premalignant.

Solar, actinic or senile keratoses

These lesions may be called by several names, but they usually can be identified by the following characteristics: the typical lesion is flat or slightly elevated, of a brownish or reddish color, papular, dry, rough, adherent, and sharply defined. They commonly occur as multiple lesions, chiefly on the exposed portions of the skin.



Patient P.T. seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.*

Sequence of therapy/ selectivity of response

After several days of therapy with Efudex® (fluorouracil), erythema may begin to appear in the area of the lesions; the reaction usually reaches its height of unsightliness and discomfort within two weeks, declining after discontinuation of therapy. This reaction occurs in affected areas. Since the response is so predictable, lesions that do not respond should be biopsied.

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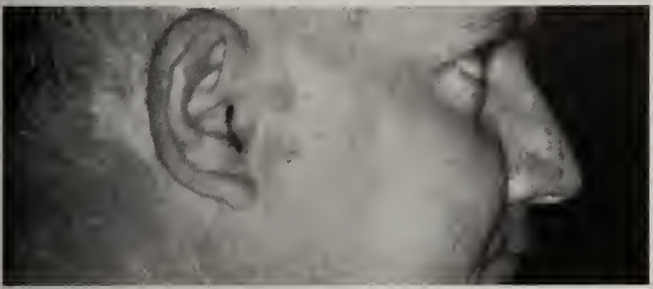

Patient P.T. seen on 6/12/67, seven weeks after discontinuation of 5%-FU cream. Reaction has subsided. Residual scarring not seen except for that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.*

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.
Contraindications: Patients with known hypersensitivity to any of its components.
Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.
Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.
Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.
Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.
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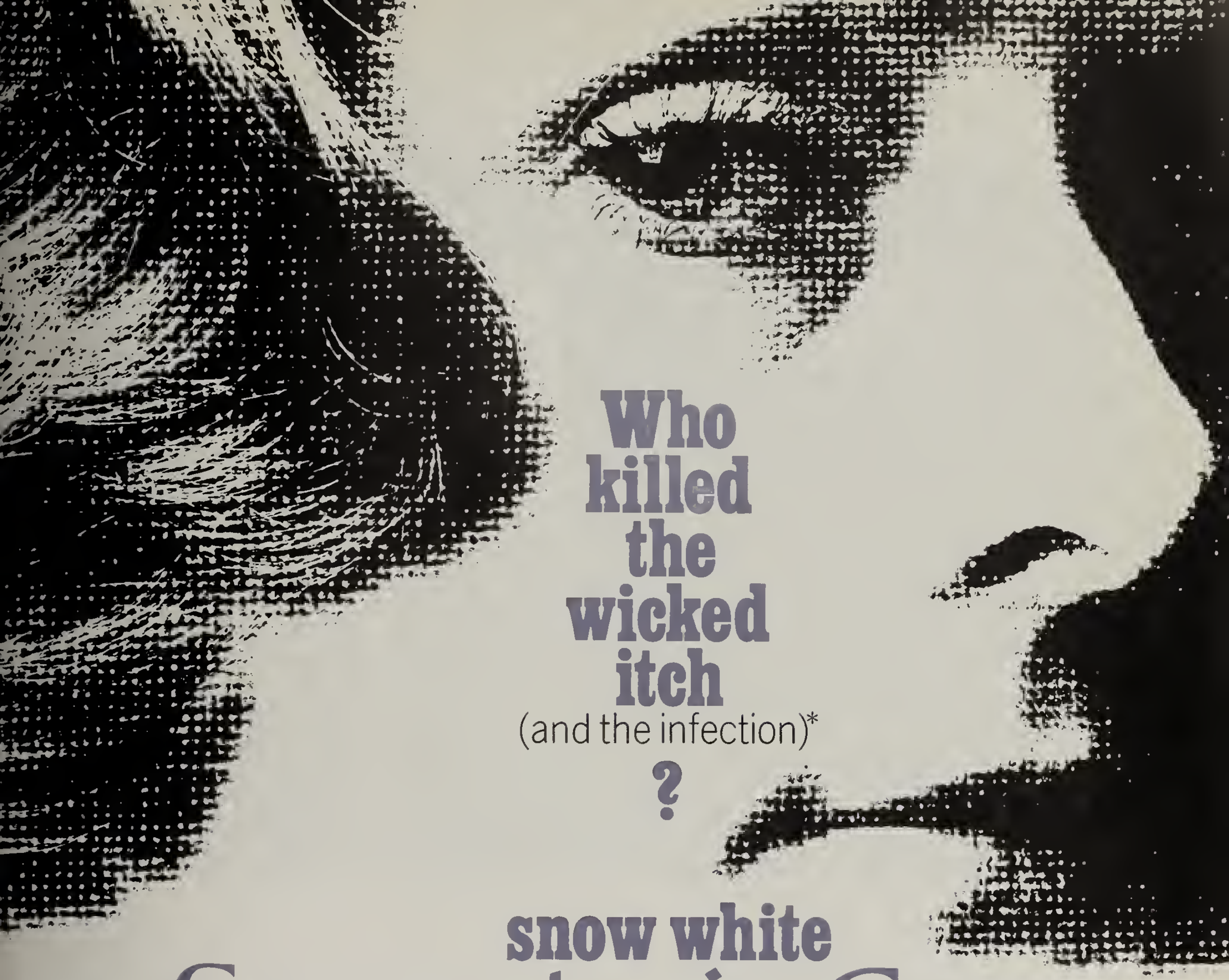

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two tubes...two weeks

* **Indication:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication as follows:
"Probably" effective: For the treatment of vulvovaginal candidiasis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: None known. **Precautions:** Cases of sensitization and irritation have been reported. When noted the drug should be discontinued. **Dosage:** One applicatorful intravaginally twice daily for a period of 14 days. Course of therapy may be repeated if necessary.

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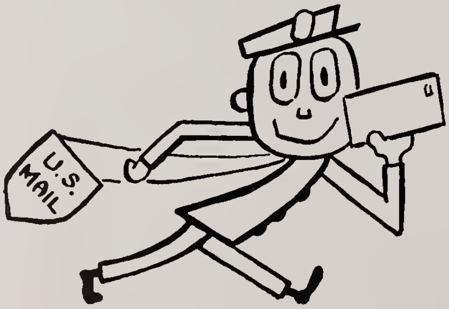

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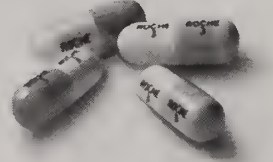

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use of potentiating drugs such as MAO inhib
and phenothiazines. Observe usual precautio
presence of impaired renal or hepatic functio
Paradoxical reactions (*e.g.*, excitement, stimul
and acute rage) have been reported in psychi
patients and hyperactive aggressive children.
Employ usual precautions in treatment of an
states with evidence of impending depressio
suicidal tendencies may be present and prote
measures necessary. Variable effects on blood
coagulation have been reported very rarely
patients receiving the drug and oral anticoag
lants; causal relationship has not been establi
clinically.

Adverse Reactions: Drowsiness, ataxi
confusion may occur, especially in the elderly
debilitated. These are reversible in most insta
by proper dosage adjustment, but are also occ
sionally observed at the lower dosage ranges.
few instances syncope has been reported. Als
countered are isolated instances of skin erupt
edema, minor menstrual irregularities, nause
constipation, extrapyramidal symptoms, incr
and decreased libido—all infrequent and gen
controlled with dosage reduction; changes in
patterns (low-voltage fast activity) may appe
during and after treatment; blood dyscrasias
cluding agranulocytosis), jaundice and hepat
dysfunction have been reported occasionally,
ing periodic blood counts and liver function
advisable during protracted therapy.

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SCIENTIFIC ARTICLES

Choledochoduodenal Fistula A Rare Complication of Duodenal Ulcer Report of Three Cases Charles E. Bickham, Jr., M.D., F.A.C.R 217

Carcinoembryonic Antigen (CEA): A Review and Current Status George P Blundell, M.D., Ph.D 222

Congenital Bronchoesophageal Fistula in the Adult. Report of Three New Cases William S. Lyons, M.D., M.S. (Surg) and Michael G Seremetis, M.D 225

Provision of Emergency Health Care at a Rock Festival. Charles R. Hayman, M.D., Raymond L. Standard; M D, Hibbs S. Meek and Mary J. Berkeley 229

Automatic Ultrasonic Measurement of Brachial and Popliteal Blood Pressures for Health Testing. Cesar A Caceres, M.D., Barbara Siebelt, R. N and Howard M Hochberg, M D 234

OTHER FEATURES

The View Box 221

ECG Problems 233

New Members 241

Book Reviews 245

- Radiologic Examination of the Urinary Tract (Pollack) Reviewed by Martin A. Thomas, M.D., F.A.C.R
- Progress in Clinical Pathology, Vol IV (Stefanini) Reviewed by Walter E. Lawrinson, M.D.
- The Pathogenesis of Atherosclerosis (Wissler and Geer) Reviewed by John C. LaRosa, M.D.
- The Psychoanalytic Study of Society (Muensterberger and Esman) Reviewed by Bernard Mathis Malloy, M.D.
- Emergency Room Diary (Rubin) Reviewed by Raymon A. Noble, M.D.

(continued)

Surgical Pediatrics (Gans) Reviewed by Richard M. Schisgall, M.D

Artificial Organs and Cardiopulmonary Support Systems (Rapaport and Merrill) Reviewed by Karel B. Absolon, M.D., Ph.D.

Lipids, Malnutrition and the Developing Brain (Ciba Foundation Symposium) Reviewed by A. Earl Vivino, M.D.

Obituaries 261

Classified Advertising 15

Information for Authors 14

Index of Avertisers 16

Advertising and Subscription Information 14

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PRESIDENT'S MESSAGE

Irving Burka, M.D.

Health, Welfare, and Politics

During the Sixties when the ideas for the Great Society were being formulated, the Administrations of that time, imbued with the spirit of creating a better, healthier and economically more stable society, began in earnest to funnel funds into various innovative projects. The aim, particularly regarding health care, was the funding of categorical projects for heart, kidney, blood pressure, cancer, and many others; investigation of various health care delivery systems; aid to education, and so forth. Grants were made, Regional Medical Programs created, and monies for construction of new medical schools and hospitals, as well as the remodelling and adding to old ones, were made available.

Thus, there came about a subtle blending of Government, Medicine, and Community for the purpose of improving the health and welfare of all the people. What a wonderful utopic dream!

The present administration has concluded that these worthwhile activities are unnecessary, superfluous and a waste of the tax dollar. Hence, the ukase that they must be phased out by a certain fiscal date. In this manner we have made a complete circle from too much bounty to none at all. Thus it is with politics. This is not to say that there has not been some waste, overlapping and poorly coordinated programs, due, frequently, to Government and political bureaucracy. However, to condemn all of the worthwhile programs to limbo, because of the need for better coordination and management, is incredible.

We need more, not less help for the poor, mentally ill, and aged. We need more, not less in the field of health, education and retraining. We need more help, not less in the funding of research in the disease entities described above.

Now we, who are concerned, must go hat in hand, pleading and praying as a beggar for a morsel here and there, just to prolong the life of a few of the most necessary projects.

"Where there is no vision, the people perish."

IRVING BURKA, M.D.

For an organization supposedly opposed to change, the AMA has made a lot of changes.

One of the most significant was the addition of an important new voice in the AMA—that of interns and residents. For the first time, these young physicians have not only a voice but also a vote in helping shape AMA policies.

Recently, the AMA House provided the same opportunities for membership and participation to medical students.

That's not all. In another important change, the AMA's council-committee structure has been streamlined. Some councils and committees have been dropped. Others have been made more efficient by reducing their size to seven members for councils and five for committees. And to permit more frequent infusion of new members and ideas, maximum tenure of service has been reduced to seven and five years, respectively.

The AMA *has* made a lot of changes. Changes to make it more responsive to the ideas of *all* physicians . . . changes to make it more effectively serve the needs of the profession.

Change will continue. But it will be decided only by those of you interested and dedicated enough to be a force in that change.

Join us.
We can do much more together.
American Medical Association
535 N. Dearborn St./Chicago, Ill. 60610

EdITORIAls

American medicine is living in a period of turmoil and evolution.

The amazing advances in science and technology together with practically instant communication, have been responsible in some degree for the unrest. Change in living habits, behavior and morals has added to it. In addition the always increasing spectre of third party intervention in the practice of medicine, be it an insurance carrier or the government, has added to the problems affecting the equanimity of the profession.

Every physician has felt the unrest caused by these circumstances and in his own way has tried to meet them. Continuing education has for the most part enabled him to keep somewhat abreast of the torrent of new knowledge and skills without which he would soon become obsolescent.

Specialty societies have had their largest growth during this period. Because of their ability to narrow in on a particular segment of medicine, they have been able to maintain the professional expertise of their members. However, they do not offer the solutions which will enable the profession as a whole to meet the challenges which confront it since they, by their nature, limit their interests.

Without detracting from specialization in any way, I would say that specialty societies cannot serve as the spearhead of the profession. Allies, yes, and important ones too; but far better in the supporting role.

To meet the present day problems in the delivery of health care, to protect both the public and the profession from the encroachments of government and third parties and to maintain a reasonable patient-physician relationship, an overall, unifying organization is required. The experience of the profession in England at the time the National Health Service was started should be example enough. Wedges were driven in between the various colleges, representing specialties, splitting them away from the British Medical Association with a result well known. The same thing could happen here if the profession allows it.

There is a very good alternative, however. Already existing is an organization designed to be the overall, unifying one and which can be the spearhead for the profession. This, of course, is the American Medical Association which exists for the purpose of improving the quality and delivery of medical care in all of its aspects.

What, exactly, is the American Medical Association? It is a federation of state associations which are composed of county societies. The county societies, in turn, are composed of individual members. Basically, then, the AMA is made up of its members organized to carry out its various responsibilities. How well these responsibilities are carried out depends on the interest and efforts of its members.

County and state society organizations parallel the national. Problems of county and state societies are similar to those facing the national society. The difference here lies in the level at which the problems must be faced. This in turn indicates the scope of the problem, though not necessarily its content. As an example, county and/or state societies deal directly with local Blue Shield Plans regarding fees, service, etc. Through its members on the Board of the National Association of Blue Shield Plans the AMA seeks to resolve any problems that can only be solved at that level while at the same time offering such support and information as is necessary to the counties and states.

Confronted by such myriad problems as National Health Insurance, Professional Services Review Organizations, Health Maintenance Organizations and unionism, to mention only a few, the AMA has been steadily taking steps to meet and contain the problems.

Improved communications with individual members is a primary goal. The membership opinion poll of last year, now being repeated, the publications received, and meetings with groups of members in an eyeball to eyeball type of confrontation are some of the methods used. Inclusion of representatives from the specialty societies, residents and interns and students among the members of the House of Delegates broadens the base from which it operates.

The introduction of national legislation designed to improve the quality and availability of health care by a number of mechanisms has given the AMA an entirely different posture. From being an organization reacting only to the proposals of others, it has become an advocate organization. This has made the Association much more effective in supporting its position when dealing with the Congress or the administrative branches of government.

As said before, the interest and efforts of its members are essential for success but individuals cannot influence the performance of government. Only a strong national organization with its strength derived from a united membership can monitor government and represent all of those it serves, the public and its members, while doing so.

If our profession is to pass through the current period of turmoil and evolution in an orderly fashion, maintaining its integrity and fulfilling its responsibilities it must be represented by some organization.

The only organization which we as a profession possess which can in any way be that representative is the American Medical Association.

RAYMOND T. HOLDEN M.D.

Sally's back in sew biz! After an arthritic flare-up.

tant Note: This drug is not a simple analgesic. Do
lminister casually. Carefully evaluate patients be-
tarting treatment and keep them under close su-
ion. Obtain a detailed history, and complete
cal and laboratory examination (complete hemo-
urinalysis, etc.) before prescribing and at fre-
intervals thereafter. Carefully select patients,
ng those responsive to routine measures, contra-
ited patients or those who cannot be observed fre-
ly. Warn patients not to exceed recommended
je. Short-term relief of severe symptoms with the
est possible dosage is the goal of therapy. Dosage
d be taken with meals or a full glass of milk. Sub-
e alka capsules for tablets if dyspeptic symptoms
Patients should discontinue the drug and report
diately any sign of: fever, sore throat, oral lesions
otoms of blood dyscrasia); dyspepsia, epigastric
symptoms of anemia, black or tarry stools or other
ence of intestinal ulceration or hemorrhage, skin re-
ns, significant weight gain or edema. A one-week
eriod is adequate. Discontinue in the absence of a
able response. Restrict treatment periods to one
in patients over sixty.
ations: Acute gouty arthritis, rheumatoid arthritis,
natoid spondylitis
raindications: Children 14 years or less; senile pa-
s; history or symptoms of G.I. inflammation or ul-
ion including severe, recurrent or persistent dys-
a; history or presence of drug allergy; blood
asias; renal, hepatic or cardiac dysfunction; hy-
nsion; thyroid disease; systemic edema,
atitis and salivary gland enlargement due to the
polymyalgia rheumatica and temporal arteritis;
nts receiving other potent chemotherapeutic
ts, or long-term anticoagulant therapy.
ings: Age, weight, dosage, duration of therapy, ex-
ce of concomitant diseases, and concurrent potent
otherapy affect incidence of toxic reactions. Care-
nstruct and observe the individual patient, espe-
the aging (forty years and over) who have
ased susceptibility to the toxicity of the drug. Use
st effective dosage. Weigh initially unpredictable
its against potential risk of severe, even fatal, re-
ns. The disease condition itself is unaltered by the
Use with caution in first trimester of pregnancy
n nursing mothers. Drug may appear in cord blood
reast milk. Serious, even fatal, blood dyscrasias,

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including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement (B)98-146-070-G

Serious side effects do occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions

For complete details, including dosage, please see full prescribing information.

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Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

BU 8615-9

What should a medication for sleep be expected to provide?

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychologica dependence have not been reported on recommended doses, use caution in administering to addiction-prone individual or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effect Employ usual precautions in patients who are severely depressed, or with

for 7 to 8 hours without need to repeat dosage during the night

No sleep medication has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia patients given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer nighttime awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to repeat dosage during the night.

with consistency

Dalmane (flurazepam HCl) has been shown to be consistently effective even during consecutive nights of administration. Thus there is little likelihood for the need to increase dosage to maintain therapeutic effect.

Dalmane is in a class by itself. Not a narcotic, barbiturate or methaqualone, Dalmane is the only available benzodiazepine specifically indicated for insomnia.

with relative safety

Chronic tolerance studies have confirmed the relative safety of Dalmane (flurazepam HCl); no depression of cardiac or respiratory function was noted in patients administered recommended or higher doses for as long as 90 consecutive nights. In most instances when adverse reactions were reported they were mild, infrequent and seldom required discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. Dizziness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

When your evaluation of insomnia indicates the need for a sleep medication, consider Dalmane—a single entity agent proved effective and relatively safe for relief of insomnia.

DALMANE®
(flurazepam HCl)

When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

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ROCHE LABORATORIES
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Nutley, New Jersey 07110

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nt depression or suicidal tendencies.
iodic blood counts and liver and kid-
function tests are advised during
eated therapy. Observe usual precau-
is in presence of impaired renal or
atic function.

erse **Reactions:** Dizziness, drowsi-
s, lightheadedness, staggering, ataxia
falling have occurred, particularly
lderly or debilitated patients. Severe
ation, lethargy, disorientation and
ia, probably indicative of drug intoler-
e or overdosage, have been reported.

Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American Pharmaceutical Association

"Too many doctors are indiffe ent to the economic consequences their decisions." So stated a recent issue of *Medical News Report* (December 4, 1972), an independent weekly newsletter published by form AMA Chief Executive F. J. L. Blasingame, M.D.

Doctor, are you indifferent...?

In discussing an anticipated in crease in Blue Shield rates, Dr. Blas ingame's newsletter had this to say:

"In general, it can be said, MD' have given the impression they are not particularly concerned with the increase in cost of health care to the patients...

"True, an MD's training is primarily scientific, but in the real worl of practice, all of his scientific decisions have a price tag, or an econom impact. The economics of health ca beckon the practitioner's attention. Concern for economics of medicine

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical Manufacturers Association

When the pharmacist recommends that a drug product other tha the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is nece sary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, the unilateral decision of the pharmacist made in the absence of clinical know edge of the patient, could expose him to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothin in the pro-substitution argument that offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowledg about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degree puts him at a disadvantage. Most often, a practicing physician will nee expert knowledge of no more than 25

Advertisement

ould be an obligation of medical actice…

"Medical societies ought to con- ct continuing campaigns to point t the substantial savings that could realized thru deductible insurance d protection for catastrophic ill- ss. At the very least, they should, in e patients' interest, question the ctics of any insurance organization at raises health care costs by forc- g policyholders to buy insurance ey may not need or want and prob- ly won't ever use.

"Too many doctors are indiffer- t to the economic consequences of eir decisions. Too many, for ex- nple, habitually hospitalize patients r the convenience of the MD. It's nsense to deny such habits exist…

"Doctors, thru their medical so- eties, have unhesitatingly appealed their patients for support in the ght against government interference th the private practice of medicine. nd the public in the past has re- ponded. It's time the American Med- al Association and state and local edical societies paid off the debt by ecisive action to hold down the cost medical care."

ost of Drugs

Insurance rates and hospital narges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned*. Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

---

30 drugs that he selects to treat the ajority of conditions encountered in s practice. Moreover, the physi- an's choice of a specific brand is ased on his knowledge of the pa- ent's medical history and current ondition, and his experiences with e particular manufacturer's roduct.

Some substitution proponents ave argued that the dispensing of a rescription is a simple two-party ansaction between the pharmacist nd the patient, and that a substitut- g pharmacist may avoid even a chnical breach of contract by simply otifying the patient that he is making e substitution. I would judge that w courts would be sympathetic ward a pharmacist who substituted ithout physician approval and who ndertook a legal defense that seeks make the patient responsible for e pharmacist's actions.

educed Prescription Prices?

Substitution advocates are uggesting to the consumer, and par- cularly the consumer activist, that educed prescription prices could ollow legalization of substitution. e have seen absolutely no evidence justify this claim. To the contrary, xperience in Alberta, Canada, where ubstitution is authorized, suggests the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands—of, say, ampicillin or tetracycline—or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

Pharmaceutical
Manufacturers Association
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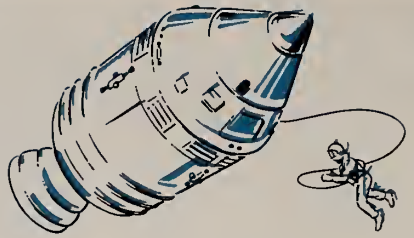

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Choledochoduodenal Fistula: A Rare Complication of Duodenal Ulcer
Report of Three Cases

CHARLES E. BICKHAM, JR., M.D., F.A.C.R.*

A rare complication of peptic ulcer disease is perforation of a duodenal ulcer into the biliary ducts, producing a choledochoduodenal fistula. Clinical recognition is difficult, because the symptoms are those of chronic peptic ulcer, and the patient may be treated medically for a long time before the condition is recognized either by roentgenologic studies, surgery, or autopsy.

According to Kyle, the first case report of choledochoduodenal fistula due to duodenal ulcer was published by Long in the London Medical Gazette in 1840.[1] In 1965 Kouriasis and Chouliaras stated that there were 149 cases in the world literature.[2] Constant and Turcotte in 1968 found 28 cases in the American literature and added seven from the University of Michigan Medical Center.[3]

This paper reports three cases of this rare manifestation of peptic ulcer and reviews the pathology, clinical features, roentgenologic findings and treatment. Suggestions for arriving at the diagnosis will be proposed.

Report of Cases

Case 1. (J. P. K.) This 51 year old white man was admitted to Doctors Hospital on February 1, 1968, with vague indigestion, weakness and the passage of a tarry stool. There was an 11 year history of recurrent duodenal ulcer.

On February 3, 1958, an upper gastrointestinal study was done. (Fig. 1) The preliminary abdominal film showed no abnormalities and no air was noted in the biliary tract. The esophagus and stomach were normal. The first portion of the duodenum was extremely deformed and contracted to such an extent that it was impossible to determine whether an ulcer were present. A fistula between the first portion of the duodenum and the common bile duct permitted immediate filling of the upper common bile duct, portions of the hepatic ducts, and the cystic duct. There was no filling of the distal common duct. The mucosal pattern of the descending duodenum was smooth and the duodenum appeared to have extrinsic pressure upon its medial side, which caused it to be displaced to the right and posteriorly by the pancreas. A repeat cholecystogram done on February 8, 1958, showed good function and no stones.

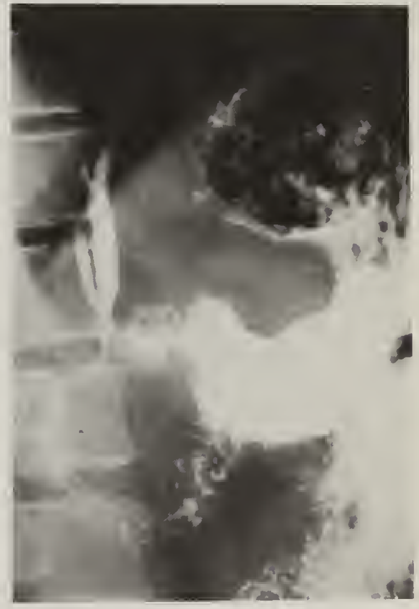

FIG. 1. (J. P. K.). Upper gastrointestinal study on February 3, 1958, showing extreme contractile deformity of the first portion of the duodenum. A fistula between the duodenum and the common bile ducts permits filling of this structure and portions of the hepatic ducts. There is also filling of the cystic duct. The distal portion of the duodenum does not fill apparently due to enlargement of the pancreas which is pressing upon and displacing the descending duodenum to the right.

Subsequent surgical exploration revealed the duodenum to be bound down in a mass of scar tissue apparently emanating from an ulcer in the first portion of the duodenum. A subtotal gastric resection was performed, leaving the duodenal area untouched. The final diagnosis was of duodenal ulcer with bleeding, obstruction and perforation into the biliary system. The patient was discharged on March 2, 1958, improved. No follow up radiological studies were obtained.

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Case 2. (R. S.) This 71 year old white man was admitted to Doctors Hospital on September 2, 1969, complaining of epigastric distress at bedtime. For the past three months he had received peptic ulcer medication with very little relief. There was a history of duodenal ulcer of many years duration. On September 4, 1969, an upper gastrointestinal study showed extreme deformity, marked narrowing, and a 1.3 cm. ulcer crater on the posterior wall of the first portion of the duodenum. There was no filling of the bile ducts with barium or with air.

A repeat upper gastrointestinal study on September 11, 1969, resulted in filling of the proximal portion of the common bile duct, the cystic duct, and a portion of the gall bladder. This filling indicated a fistulous communication between the first portion of the duodenum and the bile ducts. (Fig. 2) Review of an upper gastrointestinal series done May 17, 1965, showed barium in the common bile duct, and it is postulated that this fistulous tract could have been present for over four years. (Fig. 3)

When surgery was performed and the duodenum opened, an ulcer was found posteriorly perforated into the common bile duct. A Finney pyloroplasty was accomplished, followed by a bilateral vagotomy. There was a good recovery and the patient was discharged from the hospital on September 28, 1969.

A follow-up upper gastrointestinal study on November 3, 1969, showed marked deformity of the first portion of the duodenum, but no evidence of ulcer nor of fistulous communication with the common bile duct and its tributaries. (Fig. 4)

Case 3. (H. W.) This 60 year old white man was admitted to Doctors Hospital on May 31, 1970, for operative treatment of a penetrating duodenal ulcer. He had suffered from chronic ulcer symptoms for many years, which in the spring of 1970 became aggravated by intractable vomiting. An upper gastrointestinal series on April 14, 1970, showed an ulcer of the duodenum with penetration and filling of the common bile duct with barium. He was treated medically with some improvement in his symptoms. However, a follow up gastrointestinal study on May 26, 1970, showed filling of the bile ducts and also filling of the pancreatic duct. (Fig. 5)

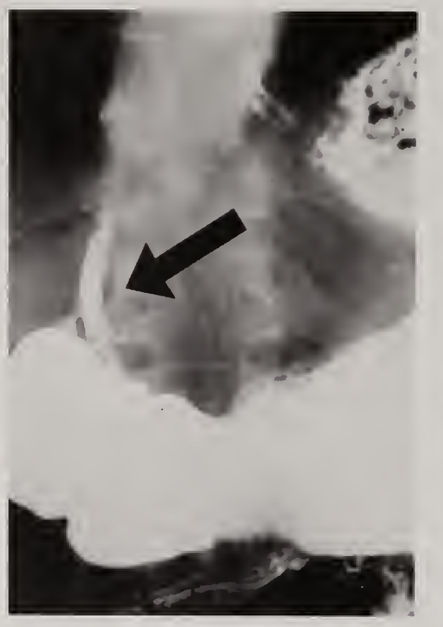

FIG. 2. (R. S.). Upper gastrointestinal study on September 11, 1969, shows the common bile duct (arrow) filled with barium due to a fistula between the first portion of the duodenum and the bile duct the result of penetrating peptic ulcer.

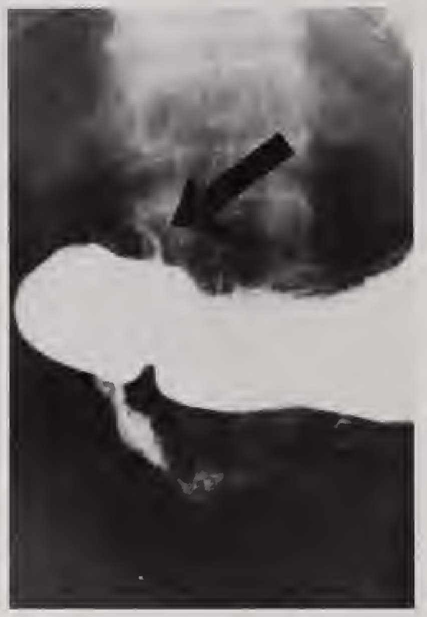

FIG. 3. (R. S.). Review of an upper gastrointestinal study done on May 17, 1965, shows filling of the common bile duct (arrow). The filled duct was overlooked at that time.

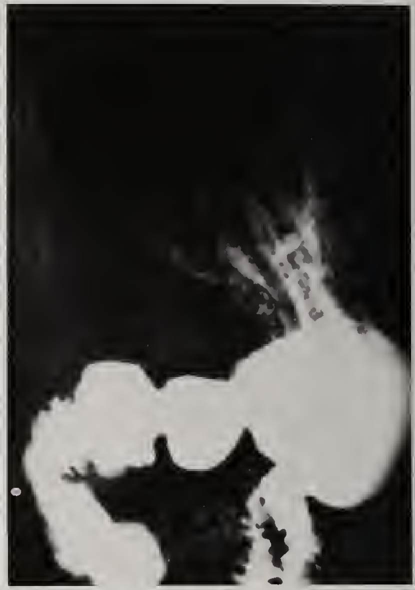

FIG 4. (R. S.). Follow up study on November 3, 1969, following surgery reveals no evidence of the fistula or filling of the biliary ducts.

Surgery was recommended, and on June 2, 1970, under general anesthesia an exploration was carried out. This revealed a contracted, indurated pancreaticoduodenal area, which lay well posterior, fused to the gastro-hepatic omentum and to the posterior abdominal wall. The duodenum was not dissected free because of these findings. A subtotal gastrectomy was performed and a Bancroft exclusion procedure was carried out with excision of the antral mucosa. Post operatively he did well and was discharged on June 9, 1970. No follow up radiological studies were performed.

Pathology

Recurring or chronic peptic ulcer probably accounts for most choledochoduodenal fistulas, although rarely an impacted gall stone in the common bile duct may erode the duct and perforate into the duodenum. Less common causes of choledochoduodenal fistulas are trauma or malignant disease.

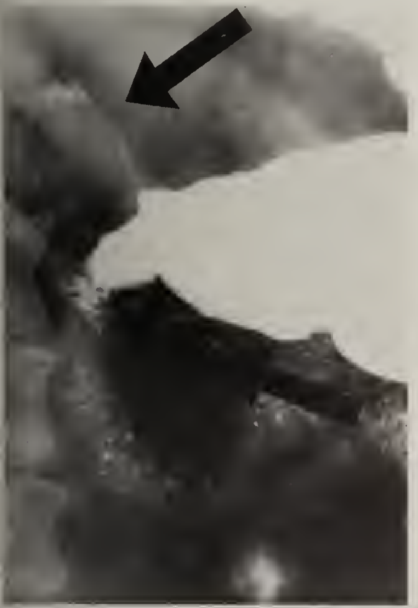

FIG 5. (H. W.). Upper gastrointestinal study on May 26, 1970, shows filling of the common bile and cystic ducts (upper arrow). The lower arrow indicates barium in the pancreatic duct.

Posterior wall duodenal ulcers are common and penetration into the pancreas is not unusual. The low incidence of fistulous communication is somewhat surprising in view of the frequency of posterior wall ulcers. Since the clinical manisfestations are few and subtle, this type of perforation often is unrecognized and may be more common than realized.

After penetration of the ulcer into the head of the pancreas an inflammatory reaction occurs, resulting in the release of destructive pancreatic enzymes which predispose to fistula formation. Penetration of the ulcer into the hepatoduodenal and hepatogastric ligaments may rarely obstruct the proximal portion of the common bile duct. Localized cholangitis and peritonitis occurs around the biliary tract. Diffuse cholangitis and hepatitis are apparently rare, since experimental anastomosis between the bile ducts and duodenum produced little liver damage—in spite of a large reflux through the fistula—because of the remarkably sterile contents of the duodenum.[4] The distal end of the common duct may become obstructed by the inflammatory reaction in the pancreas. In addition to formation of a fistula, the marked inflammatory reaction at the site of the fistulous opening may be so severe that an actual stenosis and obstruction of the duodenum results with marked hypertrophy of the pyloric musculature. A massive gastrointestinal hemorrhage may occur, further complicating the pathologic picture.

Clinical Features

Choledochoduodenal fistulas occur almost exclusively in men with an average ulcer history of eleven years duration.[5] The peak incidence is in the fifth and sixth decades.[3] No specific symptoms or signs can be related to choledochoduodenal fistula secondary to peptic ulcer disease. The symptoms are those of the underlying primary disease of penetrating duodenal ulcer showing the usual complications of unremitting pain, obstruction, or hemorrhage. There is usually no history of a symptom crisis. Mild jaundice very rarely occurs at the time of the development of the fistula, but quickly clears once the opening is established. Also, as soon as the fistula is formed the alkaline bile drains into the duodenum, neutralizing the acid juices. This may produce relatively mild clinical manifestations so that the complication may be unrecognized for months or years.

Roentgenographic Findings

The diagnosis of choledochoduodenal fistula is usually made incidentally during roentgenologic studies. The two most reliable roentgen signs are the demonstration of a fistula during an upper gastrointestinal study or the finding of air in the biliary tree. It is also possible, while doing an intravenous cholangiographic study, to demonstrate a frothy excretion within the hepatic radicles, which is suggestive of a biliary fistula.

Differential Diagnosis

Although one of the most uncommon diseases affecting the upper gastrointestinal tract, most internal biliary fistulas are secondary to gall bladder disease. They are almost always symptomatic in contrast to the silent choledochoduodenal fistula due to penetrating duodenal ulcer. Cholelithiasis and cholecystitis produce cholecystoduodenal, cholecystogastric, and cholecystocolic fistulas and these comprise ninety per cent of all spontaneous internal biliary fistulas.[6]

Gas or opaque material from the intestinal tract in the biliary ducts or gall bladder usually represents a very important intra-abdominal abnormality. Air may reflux through the ampulla because of a patulous ampullary orifice, the sphincter of Oddi having been rendered incompetent by carcinoma of the ampulla, calculi in the ampulla or duodenal ulcer. Rarely no cause is found.

Fistulas may occur secondary to operative procedures on the common bile duct. Also, a purposeful fistula may be created by surgery between the bile ducts and the intestine.

Carcinoma of the biliary tract, pancreas, duodenum or sarcoma may also produce internal fistulas.

Treatment

There is no consensus regarding the proper management of choledochoduodenal fistula.[3] These fistulas of peptic ulcer origin apparently require individualized selective therapy and many personal factors determine whether the treatment will be medical or surgical.

Medical therapy alone has been advocated for the control of the ulcer diathesis.[7] Circumstances dictating this type of therapy would include good patient acceptance, relief of symptoms, and absence of further complications. Medical treatment is preferable for poor operative risks and some patients have been managed for as long as eleven years on a medical regimen.[3]

Surgery should be considered for patients showing no response to medical treatment. In patients with peptic ulcer complications such as obstruction, bleeding, and further performation, surgery is indicated. Secondary complications in the biliary tract such as ascending cholangitis or hepatitis may require operation.

There is considerable variance concerning the type of surgical procedure to be employed. It is generally agreed, however, that exposure and attempts to resect and to repair the fistula at the time of surgery are usually unwise.[8] The Bilroth II gastrectomy is a preferred surgical approach, because it limits the possibility of reflux through the choledochoduodenal fistula. Others advocate a Bilroth II subtotal gastric resection and choledochostomy with possible cholecystoduodenostomy.[5] In recent years vagotomy and gastroenterostomy have met with success because the scarred duodenum and fistulous tract can be entirely avoided.[3] Finney pyloroplasty and bilateral vagotomy have also been used with good results.

Discussion

In the past many of these fistula were thought to be due to erosion of a common duct stone and in some instances, even after surgical exploration, these have been missed.[5] In some recent medical textbooks there is no mention of the abnormality and its existence may not be known to some members of the medical profession. The diagnosis of choledochoduodenal fistula in the three cases reported in this paper was a fortuitous finding when the patients came to the hospital for the complications of chronic peptic ulcer of bleeding, intractable pain, and impending obstruction. It is possible that these fistulas are more common than was previously thought, especially in patients with long standing recurring symptoms pointing to a posterior penetration. A patient with a recalcitrant peptic ulcer should have roentgen studies to determine if such complications have developed. If the clinician thinks of the diagnosis of choledochoduodenal fistula in patients with chronic ulcer disease and in turn suggests this to the radiologist at the time of roentgen studies perhaps more of these fistula can be discovered.

Although air in the biliary tract may suggest a biliary fistula, absence of air does not rule out the diagnosis. No air was seen in the ducts of the patients reported here. The routine abdominal film may not show the bile ducts and it is suggested that localized supine and upright films of tomography of the right upper quadrant be employed in an attempt to demonstrate the gas pattern. Seidlitz powders, carbonated beverages or the use of a "straw with a hole in it" to introduce air into the stomach and duodenum might also be helpful.

The inconstant filling of the fistula with barium may be due to the size of the opening, the particle size of the opaque media and the fluoroscopic technique. When examining patients suspected of fistula, the Trendelenburg position, using gastrograffin, may show more of these than when the usual barium techniques are used.

By using the roll technique to increase the intraabdominal pressure, the opaque material in the duodenum may be forced into the fistula. The use of delayed follow up films might possibly be of some use but the continual secretion of bile may wash the opaque out of the ducts.

Summary

1. Choledochoduodenal fistula is a rare complication of peptic ulcer and three new cases have been reported.
2. The pathological changes have been described.
3. The clinical symptoms and signs are difficult to evaluate and the condition may go unrecognized for months or years.
4. The diagnosis is usually made incidental to roentgenologic studies, although occasionally it is found at surgery or autopsy.
5. The abnormality is a potential source for further complications such as cholangitis and hepatitis. Widespread perforation, obstruction, and hemorrhage may also occur.
6. It is suggested that the introduction of air into the stomach and duodenum followed by supine and upright films or tomography be employed in attempts to demonstrate air in the biliary ducts.
7. Examination of the patient in the Trendelenberg position using less viscid contrast material, such as gastrograffin, might also fill the fistula.
8. There is no unanimity to treatment and each patient requires individualized selective therapy.

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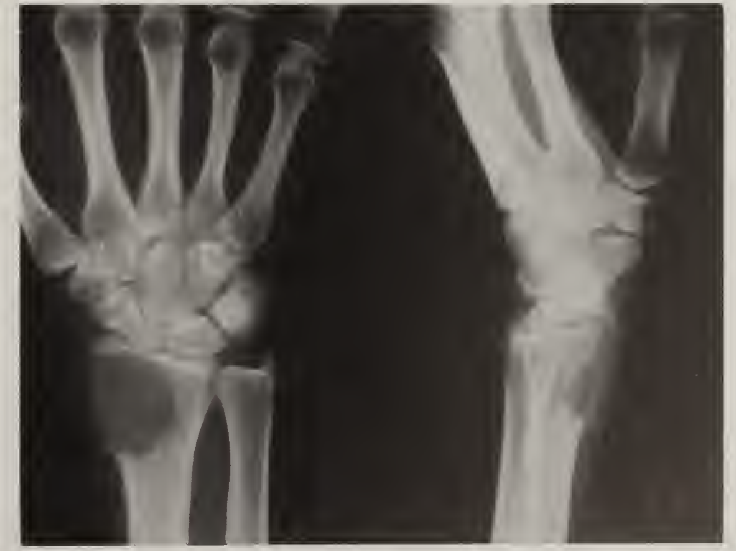
THE VIEW BOX

Prepared By
The Department of Radiology
Washington Hospital Center

This 25 year old white female complained of increasing swelling of her right wrist associated with intermittant dull aches. Clinical examination was within normal limits except for the swelling of the right wrist. Calcium, phosphorus and alkaline phosphatase levels were within normal limits.



(for diagnosis see page 224)

Carcinoembryonic Antigen (CEA): A Review and Current Status*

GEORGE P. BLUNDELL, M.D., PH.D.

Introduction

The accurate and early diagnosis of malignant disease is a great challenge to physicians, and of extreme importance.

Diagnostic tests performed in the laboratory seek to detect changes in the patient which may be the result of indirect modifications of the patient's physiology, or to detect substances which are directly produced by the tumor. Hundreds of different tests have been devised, particularly over the past 70 years. Most of the tests lack specificity, with the most specific ones those based on immunologic procedures and applied to urine, blood, tissues and body secretions.

Within the recent past, tests based on immunological principles have increased in number. Approximately eight years ago, the test devised by Dr. Phil Gold for carcinoembryonic antigen (CEA) began to receive considerable attention. However, clinical evaluations proceed slowly and all of the results are not readily apparent. A chronological survey of the developments with CEA to date is presented.

Characterization of CEA

Gold in 1965[1] reported his studies of an antigen extracted from malignant tumors of the gastrointestinal tract and the pancreas, using immunodiffusion in agar gel. The antigen was tumor-specific. In addition to the occurrence of the antigen in adult tissue, it is also present in the intestine, liver and pancreas of the fetus of two to six months gestation. In view of this, the term "carcinoembryonic" antigen was applied to this antigenic extract of the human digestive system. It is present early in fetal tissue and is repressed as the differentiation of normal digestive epithelium develops, but when the epithelium develops malignant change the antigen reappears.

By 1967[2] Gold had adapted the identification of CEA to the hemagglutination procedure, using this to determine the presence or absence of antibody to CEA. Sera from 212 human subjects were examined, and 70% of patients with malignant diseases of the digestive system which had not metastasized showed anti-CEA antibody. This was not the case with patients who had disseminated malignant disease, where antibody was detected.

Pregnant and post-partum women produce antibody to CEA antigen. The antibody also was found in two cases of non-cancerous enteric disease in this early report. It was thus shown (1) that tumor specific antibody can be produced by digestive system cancer, (2) that pregnant women produce antibody to antigens of the fetal digestive system, and (3) that this antibody may be lost if large amounts of tumor tissue develop.

In 1969[3] Vonkleist and Burton, applying the indirect fluorescent antibody technic to tissues, stained sections of tumors, peri-tumor tissue, non-tumor tissue, normal colonic mucosa, and fetal tissue. In sections of tumor and of fetal intestine they demonstrated the presence of CEA in the free membranes of the cells bordering the lumina of the glands.

It was also reported in 1969[4] by Thomson and his co-workers of the Montreal group that CEA could be identified by radioimmunoassay, in millimicrogram (nanagram) quantities. A high test value occurred in patients with a large tumor mass or metastatic spread of the primary tumor. If the tumor was totally excised at survery, the antigen could not be detected. If CEA persisted after surgery, it indicated residual tumor. If CEA reappeared several months after surgery, it was found that tumor was recurring.

In 1970[5], Hollinshead and a group of physicians at George Washington University Medical Center produced a tumor antigen from carcinoma of the colon and rectum, which was used as a skin test agent. Seventeen of 19 patients with tumor gave delayed hypersensitivity reactions. Since extracts of fetal gut produced similar reactions, they believed they were testing a CEA-like substance.

By 1971[6] Gold had studied CEA antigen by lymphocyte transformation. This test system gave no evidence of a cell-mediated immune reaction to CEA. Interestingly enough, this phenomenon should correlate with delayed hypersensitivity.

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The British workers Freed and Taylor[7] examined feces for the presence of CEA, using a gel-immunodiffusion technic, and found CEA present in the feces of 10 of 11 cases of colon carcinoma; in two of seven cases of non-colonic digestive cancer; in three of thirteen patients with non-neoplastic colon disease; and in five of 10 healthy controls.

Studies by LoGerfo[8] in New York, reported in 1972, included the reactions of 136 patients with colon carcinoma. Circulating antigen was present in seven of 19 cases with Dukes' A lesions, 14 of 23 with Dukes' B lesions, and 21 of 28 with Dukes' C lesions. Elevated antigen levels were found in 47 of 55 patients with metastatic disease. Of 33 patients with benign polyps, three had elevated CEA. Postoperatively the tumor-associated antigen decreased.

Dhar and co-workers[9] in Boston in 1972 studied CEA in 127 patients with cancer of the colon, to determine the usefulness of the test in diagnosis, prognosis, and periodic postoperative follow up. Of their Dukes' Stage A patients, three of 16 were CEA positive (19%); nine of 17 Stages B and C (53%) and 18 of 18 (100%) were positive when the tumor had metastasized to distant tissues. When CEA is not detected preoperative, the patient probably has localized tumor which can be successfully resected. A strongly reactive CEA assay suggests metastases and surgical cure is unlikely. Repeat follow-up CEA tests may detect the antigen if residual tumor grows.

The CEA test has been applied to cancers other than those of the colon, reported by Reynoso, and co-workers[10] at Roswell Park Memorial Institute, who also included carcinomas of the colon (of which 83% gave abnormal CEA levels). Patients with carcinoma of the male genitourinary system had abnormal levels in 50% of the cases in which metastases had developed. Twenty-five % of the cases of carcinoma limited to the prostate were abnormal as were twenty-four % of the bladder cases. The overall rate was 31%. One case of benign prostatic hypertrophy gave a high abnormal CEA value.

Of 41 cases of breast tumors, one of 10 with localized disease and 15 of 25 with disseminated disease gave abnormal results.

Thirty-eight % of the patients with tumors of the female genitourinary tract gave abnormal CEA levels.

Six patients of six with neuroblastoma had elevated plasma CEA levels. Four of eight cases of osteogenic sarcoma gave abnormal levels, and also two of 18 cases of multiple myeloma and one case of macroglobulinemia. Seventy % of carcinoma of the lung gave abnormal values.

This group of investigators found, as had Moore[11] and LoGerfo[12] that *100%* of their cases of carcinoma of the *pancreas* gave abnormal CEA values.

About two years ago, the National Cancer Institute and the American Cancer Society funded a project to evaluate CEA. Hospitals in Montreal, Boston, New York, and Buffalo are cooperating in this study. Interestingly enough, two different technics were permitted, with the same method of testing not used by each participant. There are variations in positivity of CEA from each series. Montreal reported 97% positivity in 36 cases; New York, 86% in 101 cases; Buffalo, 83% in 33 cases; one Boston series reported 64% in 33 cases; and at another institution in Boston several different series were reported. At this institution an initial series reported 91% positivity in 35 cases; their expanded series reported 72% in 60 cases; their present series of preresected cases reported 59% of 51 cases, and their post resection series with known tumor recurrence reported 96% positivity in 28 cases.

Conclusions

For almost ten years a tumor associated antigen, designated carcinoembryonic antigen, has been studied.

The antigen has been measured by various technics since its isolation and initial characterization by Gold. These technics include gel immuno-diffusion, hemagglutination, immunofluorescence microscopy, lymphocyte transformation, skin tests, and radioimmunoassay. The latter method is probably to be the test procedure of choice, as radioimmunoassay is sensitive enough to detect millimicrograms quantities of CEA.

A standardized C E Antigen and anti-C E serum is not at this time generally available for routine laboratory testing of patients.

The C E Antigen is extracted from pooled hepatic metastases. The extraction is technically difficult, and the most desirable method of extraction has not been developed.

The upper limit of normal for the serum level of CEA has been set at 2.5 nanograms per milliliter. This value may have to be raised to 5 ng./ml. It may also develop that fecal levels are more practical than serum levels for colon carcinoma.

At present it appears that the determination of the presence of C E Antigen in patients will be useful in (1) identifying patients with malignant disease and determining whether their tumor is localized or disseminated. It will also be useful, if the CEA level decreases after surgery, in (2) determining if tumor is recurring. The test promises to be most useful in patients with carcinoma of the colon and the pancreas.

As with all laboratory tests, patients will have to be thoroughly examined and the findings then correlated with the results of the carcinoembryonic antigen tests.

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THE VIEW BOX

(from page 221)

DIAGNOSIS: Giant Cell Tumor

The radiograph shows an expansile, excentric radiolucent lesion, fairly well circumscribed without a sclerotic rim. There is no periosteal reaction. The lesion abutts the articulating joint surface.

The patients age, symptoms, normal lab values and the radiograph strongly suggest the diagnosis of giant cell tumor. Other lesions that can present radiographically in a similar manner include aneurysmal bone cyst, fibroxanthoma and chondromixoid fibroma.

Giant cell tumors occur most frequently between the ages of 20 to 40. They are more common in females and their most common location is the distal femur, the distal radius and the proximal tibia. 20% of giant cell tumors are malignant but, radiographically, the difference between benign and malignant giant cell tumor cannot be made. The treatment of choice for these lesions is surgical excision.

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Congenital Bronchoesophageal Fistula in the Adult
Report of Three New Cases

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Introduction

Congenital communications between the gullet and the tracheobronchial tree are relatively rare. More common and better understood, because of its dramatic presentation in the neonate, is the tracheoesophageal fistula (TEF). Much less commonly seen is the bronchoesophageal fistula. The most recent series (1966)[1] numbered only 85 cases, culled from the world literature. The bronchoesophageal fistula is not so dramatic and produces, generally, chronic symptoms not distinct from other forms of chronic pulmonary disease. Characteristically, it is diagnosed after childhood. In the collected series of Blackburn and Amoury, 68 of the 85 cases were diagnosed after the age of 14.[1] In fact, symptoms severe enough to require treatment may not manifest themselves until an advanced age. Brunner[2] has reported two patients of 83 who had successful surgical closure of the fistula, and Meller[3] has reported a 75 year old. These older patients generally give a history of chronic cough or recurrent pneumonias extending over many years. Early diagnosis has been elusive.

The three cases reported below were aged 41, 59, and 83 years. The clinical presentations were brisk hemoptysis, chronic cough, and acute aspiration pneumonitis respectively. All three had successful division of the fistula, without pulmonary resection, with complete relief of symptoms. In all three, the fistula was connected to the bronchus intermedius. Case 1 was noteworthy in that the fistula was a double one, with both connections to the bronchus intermedius.

Case Reports

Case 1: M. K. 59. For six months the patient had a persistent cough and hoarseness. She was a heavy cigarette smoker. Her chest X-ray was negative. Initially, direct laryngoscopy and bronchoscopy showed bronchitis, more marked on the right. Later a history was obtained of cough associated with swallowing liquids. An esophagram produced a bronchogram and repeat esophagoscopy and bronchoscopy visualized the fistula. On the bronchial side, the orifice lay posteriorly just beyond the upper lobe bronchus on the right. It had been mistaken for an abnormally proximal superior segment bronchus at the first bronchoscopy. The rim was smooth and clean giving no evidence of inflammation.

At thoracotomy there were two short fistulas (Fig. 1) between the bronchus intermedius and the esophagus. A large esophagotomy (Fig. 2) facilitated the dissection and visualization. The fistulas were divided and oversewn with interrupted silk. The

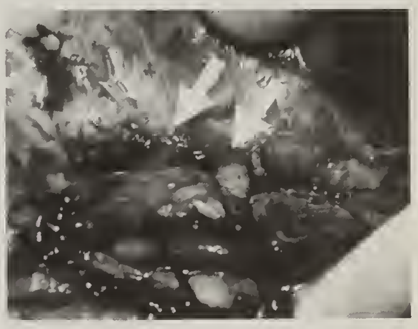

FIG. 1. Double bronchoesophageal fistula to bronchus intermedius (case I) exterior appearance. Bronchus is behind arrows; esophagus is beneath traction ligature.

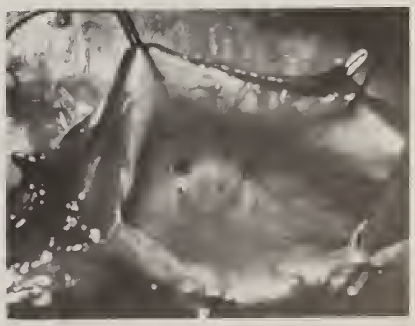

FIG. 2. Appearance of double bronchoesophageal fistula via esophogotomy (case I).

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patient made an uneventful recovery, and was grateful for having had her cough cured without having to quit smoking.

Case II: M. G., 83, complained of choking on swallowing liquids or solids for five years, worse in the preceding 18 months. There had been a 30 pound weight loss in the same period. Because of the dysphagia an esophagram was made during which aspiration of the barium was thought to have occurred. The patient was referred because of the pneumonitis which followed this aspiration, but the referring physician suspected a fistula. The patient also gave a history of persistent cough which she did not clearly associate with swallowing and for which her uvula had been excised fifteen years previously.

When admitted to the hospital a repeat esophagram clearly showed the smooth fistulous tract two cm. in length, arising from an esophageal diverticulum. Esophagoscopy and bronchoscopy were done. The fistula was visualized arising from the mid right lateral wall of the esophagus 28.5 cm. from the upper gum line. The opening was smooth, round and completely free of inflammation and completely epithelialized. The appearance was the same as the non-obstructive T.E.F. or the "H" fistula in the infant. On the bronchial side the fistula was seen as a bubbling posterior bronchial opening in the area of the superior segment bronchus.

Because of her marked distress, thoracotomy and division of the fistula were carried out. There was no evidence of mediastinal inflammation. Dissection was easy. The fistula (Fig. 3) was simply ligated and divided in the interest of speed. The patient made an uneventful recovery and was completely relieved of the symptoms which had distressed her for so many years.

Case III: D. B., 41, was first seen four years before operation for diffuse nodularity of the lungs. She had a persistent cough at that time and reported several episodes of "asthma" in the preceding two years. Three years before surgery she was seen for her first episode of brisk hemoptysis. Bronchoscopy revealed a friable mass in the bronchus intermedius which on biopsy was reported as "pyogenic granuloma." In the next nine months she was rebronchoscoped three times, each biopsy showing an inflammatory process or granulation tissue. On one occasion calcified debris was recovered. Since the patient had coughed up some of this material and her skin test for histoplasmin was positive, it was felt that broncholithiasis due to histoplasmosis was a reasonable diagnosis. Surgery was deferred because of the enormous size of the patient, her diminishing symptoms and the probability that surgery would result in the loss of her entire right lung. During the subsequent two years she got along well although the cough persisted and interfered with her singing. Two months before surgery she began to notice cough on taking liquids. Esophagram showed the fistula to the right bronchus intermedius (Fig. 4A) and selective bronchogram (Fig. 4B) with the catheter in the fistula showed that the tract was readily distensible. At bronchoscopy the granulation seen two years earlier was gone and the fistula which lay on the posteromedial wall of the proximal bronchus intermedius had a smooth epithelialized rim and looked congenital. There was no bronchiectasis. At thoracotomy the dissection was somewhat difficult, suggesting previous inflammation; however, no remarkable nodes or specific granulomatous tissue were found. A biopsy of the contiguous mediastinal tissue showed adipose tissue with surrounding fibroconnective tissue containing focal areas of lymphocytic infiltration. When the dissection was complete, a well defined muscle-covered tube was displayed which appeared entirely congenital (Fig. 5). Microscopic examination of the esophageal fistual tract revealed a fragment of tissue lined by unremarkable squamous epithelium. The underlying muscle tissue was likewise unremarkable.

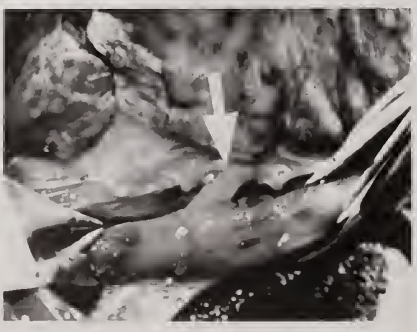

FIG. 3. Bronchoesophageal fistula in 83 year old patient (case II).

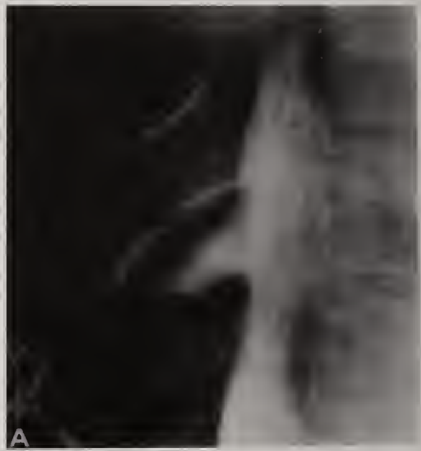

FIG. 4A. Bronchoesophageal fistula (case III) during deglutition (esophagram).

Discussion

Of the reported cases of congenital bronchoesophageal fistula, 80% are diagnosed after the age of 14 years, the median age at diagnosis being about 30 years. A number of cases have been reported over the age of 60 and prior to this report a patient age 70 and two others aged 83 had thoracotomy and division of the fistula with good results. While these patients frequently give a history of respiratory difficulties from an early age, at least half have no symptoms until well into adult life.[1] This has led to considerable speculation that these fistulas might not be fully open for some years, the opening being closed or guarded by a membrane. There has been no satisfactory evidence produced to substantiate this theory. The fistula is usually quite small and distensible, and courses cephalad from esophagus to bronchus at quite an acute angle. These anatomical features alone tend to mitigate regurgitation and probably become less effective with aging and loss of flexibility of the tissues.

Baimbridge and Keith[4] offer a classification of congenital bronchoesophageal fistulas which has some usefulness if only as an aid to remembering the various forms the abnormality may take.

Type I: A wide-necked esophageal diverticulum with inflammatory perforation into lung.

Type II: Simplest. A short tract runs directly from esophagus to bronchus.

Type III: The tract goes from the esophagus to a lung cyst which has a bronchial communication.

Type IV: The fistula runs from the esophagus to a pulmonary sequestration.

The difficulty with this classification is that in types I, III, and IV there is another prominent abnormality which could itself lead to an acquired fistula. Such was our case III, which falls into Type I. (Fig. 4A) The early findings of granulation tissue and calcium in the region of the bronchial orifice of the fistula tend to argue for inflammatory perforation from the esophagus into the bronchus. The subsequent smooth epithelialization of the bronchial orifice together with the clearly demonstrable distensibility of the fistulous tract, the presence of the large esophageal diverticulum and the well defined appearance of the fistula at surgery argue for a congenital lesion. The sequence of events in this instance point up the difficulties in interpreting the fistula as congenital when another significant abnormality is present.

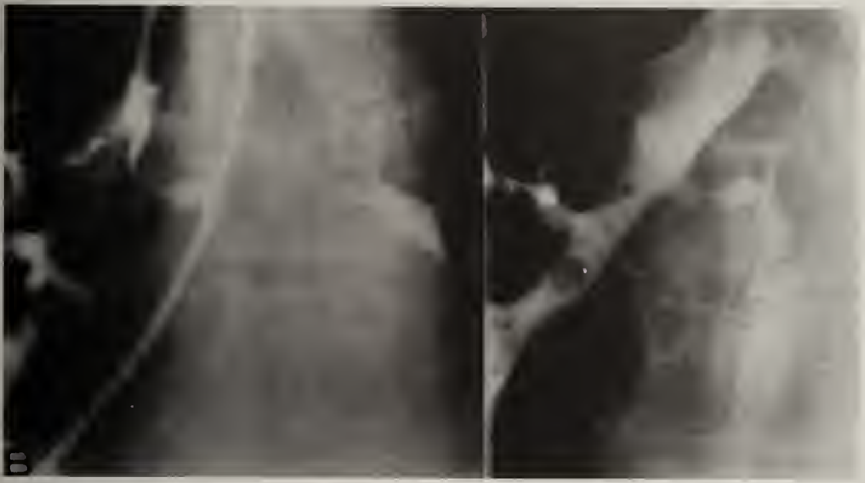

FIG. 4B. Appearance of same fistula via selective bronchography. Note that the appearance of diverticulum of the esophagus is absent when patient not swallowing (picture on right).

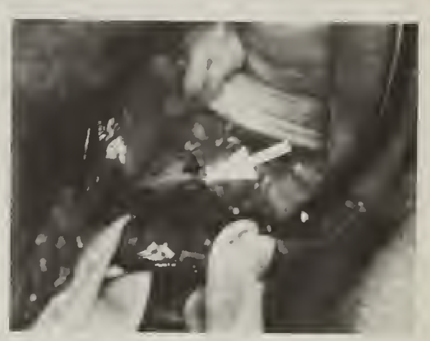

FIG. 5. Bronchoesophageal fistula at surgery (case III). Note the entirely congenital appearance of this lesion which had many features suggesting an acquired origin.

A substantial number of patients have been reported to have bronchiectasis associated with an apparently congenital bronchoesophageal fistula without the complicating features of an esophageal diverticulum, pulmonary cyst, or sequestrum. Our current understanding of pathophysiological processes involving the lung compels us to look upon the association as etiologic. The long histories together with late awareness of aspiration can be used as evidence that the fistula was acquired or secondary, although many patients are included in these same series with evidence of aspiration of many years duration without the development of bronchiectasis. On the whole, the usually well defined fistulous structure, the distensibility of the fistula reported in some cases, the epithelialization and muscular covering of the fistula frequently reported, the usual lack of surgical evidence of inflammation in the mediastinum and the lack of bronchiectasis elsewhere in the lung, would tend to indicate that the fistula causes the bronchiectasis.

The developmental origin of this anomaly is far from clear. We would agree with Frater[5] that it is difficult to postulate a similar origin for both the tracheoesophageal and the bronchoesophageal fistula; and Gerle[6] has suggested that the mechanism behind the congenital bronchoesophageal fistula and the bronchopulmonary sequestration may be the same. He refers to the fistula and the sequestration as "Bronchopulmonary Foregut Malformations" (in our opinion the term is too inclusive and non-descriptive).

The tracheoesophageal fistula occurring high up in the tracheobronchial tree is due apparently to incomplete fusion of the lateral foregut plates which are responsible for separating the trachea and gut proximal to the stem bronchi. Both Frater and Gerle believe fistulas distal to this point arise in a manner similar to the development of a bronchopulmonary sequestration; that is, from a supernumerary lung bud. However, the abnormal large systemic artery associated with sequestrations is constantly *absent*. Furthermore, it is our opinion that the sequestration which does not replace any of the normal segments or sub-segments of the lung, does not characteristically communicate with the tracheobronchial tree except secondarily through an acquired fistula.

The origin of bronchoesophageal fistulas is unsettled but from the practical surgical point of view, there are no unusual systemic arteries arising from the aorta in association with the bronchoesophageal fistulas which might offer an unexpected hazard during dissection.

Diagnosis

Early diagnosis is important to prevent recurring pneumonitis and possible bronchiectasis, and to spare the patient years of uncomfortable coughing and even useless operative procedures, such as the uvula amputation performed in Case II. Almost invariably the diagnosis of a non-obstructive esophagopulmonary fistula is made with an esophagram. A high index of suspicion leads to the performance of this examination; in most cases of the adult esophagobronchial fistula, the index of suspicion is low and cough is frequently present for years before diagnosis because of the apparent lack of relationship between the ingestion of liquids and the cough. The patient himself is often unaware of it, even when questioned in retrospect. We would suggest that at least those patients with chronic cough in whom no ready explanation for the cough is apparent, especially after bronchoscopy, should have an esophagram with water soluble media. This would certainly include those with no history of allergy, asthma, significant sputum production or smoking. Furthermore, patients with demonstrated bronchiectasis should be considered for an esophagram as part of the overall evaluation.

Case reports repeatedly indicate that lacking the certain knowledge of the existence of a bronchoesophageal fistula and its approximate location, the endoscopist will not make the diagnosis. Bronchoscopy is nevertheless very helpful in the overall evaluation and in planning the surgical approach. Bronchography, especially selective bronchography done percutaneously with the Seldinger catheter, makes possible not only the demonstration of the extent of bronchiectasis present but also a precise visualization of the fistula through catheterization of its bronchial orifice. (See Case III and Fig. 4)

Summary

Congenital bronchoesophageal fistula in the adult is rare; perhaps most are never diagnosed. Improvement in diagnosis would appear to depend upon the selection of those patients for esophagram who have no satisfactory explanation of their chronic cough and those who have demonstrated bronchiectasis. Surgical division of the fistula with concomitant resection of any diseased portion of the lung is curative and safe and should be offered to patients even of a very advanced age.

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Provision of Emergency Health Care at a Rock Festival

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Rock Festivals are a phenomenon of the past few years which have been described in detail on television and radio and in newspapers and magazine articles. Some of the articles[1] have described the medical and (un)sanitary aspects of the events, with emphasis on the pervasiveness of drug use, overcrowding, and injuries.

Very little has been written in the medical literature. Levens and Durham[2] described the health services for an outdoor 24 hour event for 40,000 people in England. Four hundred and ninety patients were treated by first aid personnel, with only 81 referred to the doctors, and only nine needing hospital emergency room care. Only eight were treated for drugs.

Taylor et al.,[3] writing on "Bad Trips", incidentally mentioned a San Jose, California festival to emphasize the use of unidentified pills. They give good rules for management including attempts to define the drugs taken, physical signs and symptoms, treatment by establishment of verbal contact (defining reality: "talking down"), use of various medications, and seeing that the patient stays with a responsible person for 24 hours.

Ahronheim et al.[4] give medical opinions following a festival at Goose Lake Park, Michigan, August 1970 involving 70,000 to 250,000. They emphasize the commercial nature of the events and that the sponsor should provide the health service or pay for it. At the same time they would have the community on disaster alert. Very much drug use was observed, but the main problem was physical trauma. In spite of the unsanitary conditions, there was apparently little spread of infection, gastrointestinal or respiratory.

This article describes a concert held in a sports stadium, with the crowd in attendance from four to eight hours.

After a two and one-half year absence, the British rock and roll group, the Rolling Stones, made their second appearance in this country. Their road tour began in June 1972, in Vancouver, continued down the West Coast, and through the mid-United States to the east. All 47,500 tickets for the rock festival in Washington, D.C. on July 4 were sold shortly after going on sale in May. 45,000 were for unreserved seats.

Planning

The Assistant Manager of the Robert F. Kennedy Memorial Stadium, contacted the Division of Emergency Health Services on June 7, and requested that we provide on site health coverage. He agreed that the D.C. Armory Board would reimburse the Department of Human Resources (DHR) for all expenses incurred.

On June 15, we attended a planning meeting at the stadium along with representatives of the Metropolitan Police, Park Police, stadium officials, and the sponsors, the Electrical Company of Philadelphia. It was suggested that five medical aid stations be set up in the stadium to handle the medical emergencies, staffed by DHR personnel and two stadium nurses, supported by one DHR ambulance and volunteer ambulances.

On June 16, we contacted the Director of the Mental Health Administration (MHA), and the Deputy Director of the Narcotics Treatment Administration (NTA), requesting that they provide the staff to handle the expected drug problems. On June 22, a second meeting was held with stadium officials, and with a representative of MHA, NTA, George Washington University Medical Center, and staff from the Emergency Health Services Division. Following an on site inspection of the facilities, it was agreed that in addition to the health staff, the Department of Human Resources would provide the following: radio communications; one ambulance with two attendants; supplies and equipment for five medical aid stations and one cardiac unit; two bedside screens; and protective masks for medical aid station personnel. We further agreed to set up a Medical Command Post at the stadium for coordination of all health activity. The stadium officials agreed that they would provide fruit juice, coffee and ice, for staff and patients.

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On June 30, we met with the Medical Director, D.C. General Hospital, (DHR) and members of his administrative staff to brief them on the plans. It was agreed that the health personnel for duty at the stadium would park in designated areas at the hospital and be transported to and from the nearby stadium by bus. We were asked to contact the Metropolitan Police and request additional protection for the hospital during this event. (We were later informed that the hospital would have to provide its own security.) It was further agreed that we would coordinate the sending of patients to the emergency department of the hospital by telephoning in advance.

Medical Aid Stations

Five medical aid stations were set up in the stadium at the following locations: one in the First Aid room, fifth level; three in the administrative office area, fourth level; and one in the First Aid room, third level. The two First Aid rooms were staffed by the stadium nurses (Table 1).

Medical Command Post

The Post was located at the switchboard, fourth level, staffed by the Chief, Emergency Health Services Division, and members of his staff. It became operational at 3:30 p.m., and was secured at 12:30 a.m., July 5.

Communications

The DHR radio network served well in providing radio communications between the Medical Command Post and personnel from the Department of Environmental Services working throughout the stadium. We were also able to keep in constant contact with the DHR ambulance and the Emergency Room at D.C. General Hospital.

Telephone communications were also available from the Post to the First Aid rooms, and proved valuable to the Police as it was the only telephone available in the area.

A Civil Defense portable radio was monitored for reports of occurrences throughout the stadium.

Comfort Stations

Three 10-unit portable toilets were placed outside the stadium entrances. The toilet facilities inside the stadium were adequate in number, although we often observed long lines of persons waiting to use the facilities.

Drinking Water

There were no vendors going throughout the stands selling soft drinks as is usual during scheduled sports events and this taxed the concession stands and drinking fountains resulting in over an hour wait in many instances for water and soft drinks. Water containers were furnished by DHR in the medical aid stations for staff and patients.

Attendance

The offical estimate from the stadium indicated that 47,500 persons, mostly white youths in their late teens or early 20's attended the concert which was the largest rock festival held in the District of Columbia in six years. About 30,000 persons were waiting when the gates were open at 4:00 p.m. Policemen at the gate entrances searched the fans and seized beer, wine, and hard liquor.

The odor of marijuana was so pungent in the stadium that it could be smelled 300 yards away. Once inside the stadium the fans were jammed into the infield so close together that many had difficulty moving their hands to applaud.

About 60 persons were arrested, approximately one-half on drug-related charges and the rest on various minor charges involving disorderly conduct and gatecrashing. Skies were sunny, and the high temperature was a relatively cool 80 degrees at 4:00 p.m. The concert did not begin until 8:00 p.m. and lasted until 10:30 p.m.

Participants and observers commented that the 200 or more police seemed more affable and relaxed than the 80 private guards on the scene. At the beginning of the festival, the atmosphere was relaxed and carefree, but as the hours passed, it became somewhat tense, and there were isolated instances of hostility. At approximately 8:30 p.m., lighted sparklers, firecrackers, and cherry bombs were being thrown into the crowd, but after about 15 minutes the crowd was again orderly.

Medical Service

Patients brought to the medical aid stations were registered at the Medical Command Post desk and then escorted to the proper treatment area depending on the complaint. Those patients unable to give the information at the desk were taken immediately for treatment and a record left with the nurse to complete. All patients were seen by the physician without waiting. This system worked well and proved to be very efficient.

On the fourth floor level, the three rooms were filled with litter cots and

TABLE I. Staffing

Medical Command Post		Medical Aid Station #1	
3 Emergency Health Services Division Staff,		1 M.D. (General)	CHHA
1 Chief, Office of Nursing	CHHA	1 M.D. (Cardiac Unit) George Washington Univ.	
On Call at Home		1 R.N.	CHHA
Associate Director for Inspection Program Analysis,	DHR	1 P.H.N.	CHHA
Associate Director for Preventive Services,	CHHA	2 Medical Assistants (Volunteer)	
Medical Aid Station #2		**Medical Aid Station #3**	
2 M.D.'s (Narcotic Specialists)	NTA	2 M.D. (Psychiatrists)	MHA
1 R.N.	CHHA	1 Ph.D. (Psychologist)	MHA
7 Counselors	NTA	1 P.H.N.	CHHA
3 Medical Assistants	NTA	1 R.N.	MHA
		1 Spanish Program Ass't.	MHA
		1 Social Worker	MHA
		2 Mental Health Aides	MHA
		2 Mental Health Technicians	MHA
		1 Secretary	MHA
Medical Aid Station #4		**Ambulance Support**	
1 R.N. Stadium Nurse		1 Ambulance DHR with driver and attendant	
		4 Ambulances from Volunteer Rescue Squads and Volunteer Fire Departments, with driver and attendant	
Medical Aid Station #5			
1 R.N. Stadium Nurse			

Medical Assistants and volunteers circulated in the crowd and brought patients to the stations. They were all young people and "hippie" types.

blankets where patients suffering from drug and/or alcohol intoxication, bad trips and similar illnesses could lie down and rest under careful observation by two physicians, two nurses, and several mental health aides. As soon as the gates were opened, this area filled and stayed busy throughout the evening. Many patients intoxicated on drugs and/or alcohol stayed in the station for four to eight hours. At the far end of the hall, a "quiet room" was set up where groups of youths sat on and under litter cots discussing their problems with mental health counselors. In the center room, "rap sessions" were in progress throughout the evening in which hippie-clad youths drank orange juice, and babbled on about anything that came to mind. They were monitored by a counselor.

At the near end of the area, a room set up to handle general medical and cardiac emergencies stayed busy until the end of the concert. Two physicians and two nurses treated a large number of patients for deep multiple lacerations of the hands and arms which occurred when the youths tried to climb on the stage. Nails and wire had been driven through the stagefront by the security force assigned to the "Rolling Stones". Five of the patients seen for this type of injury were transported for sutures to the emergency department of D.C. General Hospital.

The hallways leading to all of the rooms were often filled with those intoxicated by drugs who were being walked by mental health aides to keep them from going into a deep sleep. Frequently, patients were observed unable to get to the rest room, who had urinated, while many were vomiting on the floor and in plastic bags.

Those on bad trips were talked down by an individual counselor; a few needed physical restraint by strapping; and one needed Valium injection.

Patients Treated

A total of 221 patients were treated at the five medical aid stations, and seven were first seen at the hospital emergency room.

Eighty-four patients were treated for various injuries, of which 61 were lacerations, five requiring sutures at the hospital. About 100 were treated for symptoms related to drug or alcohol intoxication, six of these needed emergency room treatment or prolonged observation. Twenty-three were treated for the effects of gas used early in the program by the participants and not by the police (Table 2).

Comments

Several youths who were being booked by the police were brought into the medical aid station for treatment. A policeman had to stand outside the treatment room door to observe those being booked and this had a bad effect on the other patients who thought they were being arrested. A room should be set up where those being detained by the police could go without having to walk past the other patients, particularly those intoxicated by drugs. In addition patients on drugs or intoxicated with a mixture of alcohol and drugs, and those experiencing bad trips become very excitable when placed in a confining area, and it appears that they respond to treatment in a shorter period of time if left in a quiet environment, with plenty of room.

Many of the drug patients needed restraining straps. These should be stocked beforehand.

Cooperation with Other Administrations, Agencies, etc.

The cooperation between various administrations of the Department of Human Resources (Community Health and Hospitals Administration, Mental Health Administration, and Narcotics Treatment Administration) was outstanding, as was that received from the Metropolitan Police Department, Department of Environmental Health, Armory Board personnel, and the volunteer ambulance personnel.

Summary

Emergency medical services were provided for a rock festival held at the D.C. Stadium. A capacity crowd of 47,500 attended, of which 30,000 were in place four hours before the concert began.

Five medical stations were set up staffed by 33 persons, coordinated by a command post, and supported by five ambulance units.

Two hundred and twenty-one patients received treatment in the stations, including about 100 for symptoms related to drug and alcohol intoxication, and 80 for injuries of which 60 were lacerations. Five patients were sent to the hospital emergency room for sutures and three for drug and alcohol intoxication, two were kept at a mental health center for 12 hours for drug intoxication and one for alcohol intoxication. Seven patients went directly to the emergency room.

Many of the lacerations were from nails and barbed wire placed in the stage front as a barrier.

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TABLE II. Types & Numbers of Patients Treated

Lacerations	61	Drug Intoxication	30
Contusions	7	Alcohol Intoxication	4
Splinters	5	Drug and Alcohol Intoxication	2
Old wound dressed	3	Nausea and Dizziness	13
Foreign objects in eye and ear first degree burns, fractured toe, abrasions, blisters	8	Fainting	8
		Upset stomach	2
Headaches and malaise	57	Tear gas effects	23
Sore throat	2	Firecracker explosions	2
Afraid of arrest	1		
Total			228

Patients sent to D.C. General Emergency Room (Trauma 6, Intoxication 3)
Patients sent to Mental Health Centers (Trauma –, Intoxication 3)
Patients refusing to go to D.C. General Hospital (Trauma 3, Intoxication 1)
Patients treated at hospital, not sent by aid station (Trauma 5, Intoxication 2)

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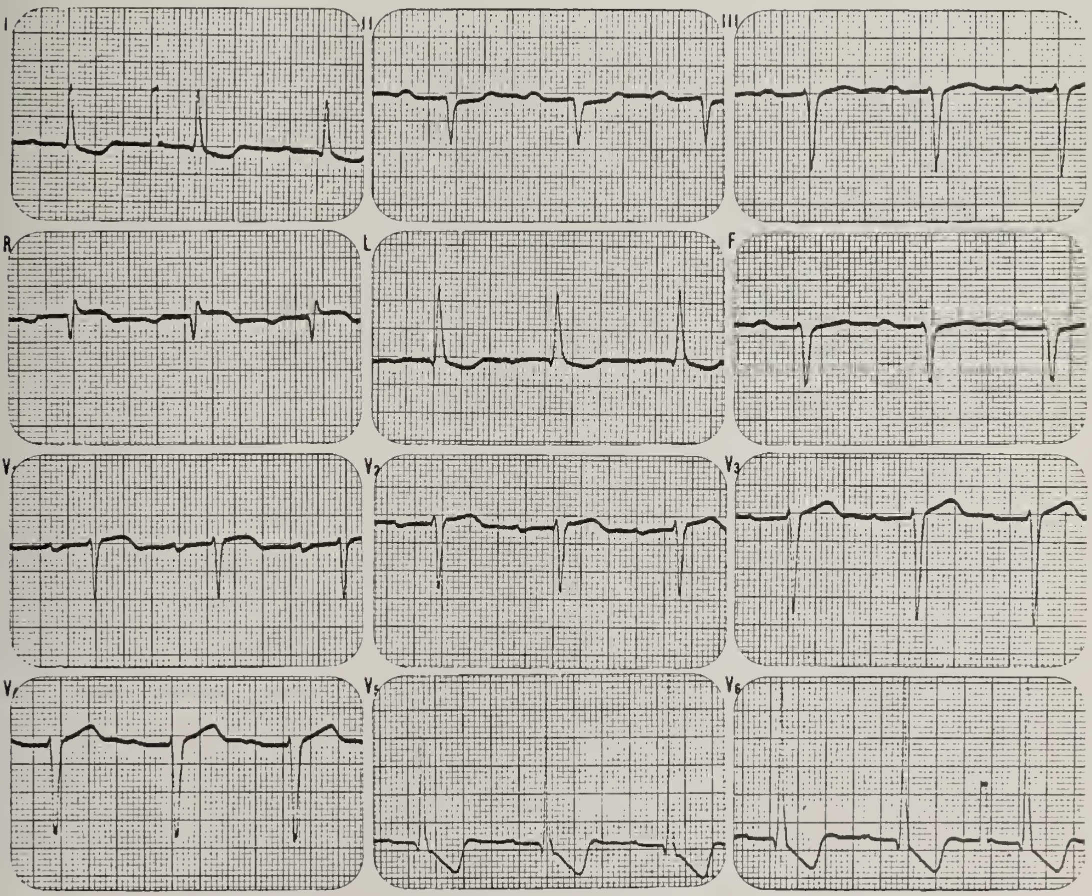
ECG Problems

HISTORY: 53-year-old male (JES) with easy fatigability but no dyspnea, or chest pain. On Digoxin 0.25 mg. daily.



(For diagnosis see page 258)

Automatic Ultrasonic Measurement of Brachial and Popliteal Blood Pressures for Health Testing*

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Health-testing systems constantly strive to amplify their disease detection spectrum. Extra cost, time and potential for care and followup are usual considerations in these attempts. In this paper we want to show the feasibility of expanding routine blood pressure (BP) to all extremities. Although our medical school textbooks suggest more, BP readings are usually limited to brachial pressure in one arm in the clinical setting.

BP determination, in addition to its role in hypertension evaluation, is a valuable measurement in the spectrum of diseases due to vascular abnormalities of extremities. Measurement of BP in both arms and legs offers the potential of adding detection of arterial obstructive disease, one of the most common problems in the elderly. It may also be useful in the evaluation of trauma to the extremities both from accidents or such stressful activity as sports. It has also been suggested that markedly lower arm than leg pressures may have an association to coronary disease.

An automatic ultrasonic BP instrument (ABPI)* proven accurate and practical for rapid mass screening of brachial pressure was used.[1-6] The sensitivity of the ultrasound system has been shown to readily detect popliteal blood pressure.[7-9] Special transducer and cuffs have been designed for the purpose and the total system validated against intra-arterial femoral pressures. A manually operated sequential multiplexer has been added to the device to allow sequential BP determinations in all limbs.

This report describes a study in an automated multitesting clinic of the practicality of adding BP in all four limbs to the sequence of screening tests. Data indicating the typical values for limb pressures and the expected differences are presented. Followup of marked discrepancies, as warranted, has been placed in the hands of the patients' private physicians.

Method

The ABPI and multiplexer (MUX) were placed next to the examining table used for blood pressure measurements. Cables containing the air and electrical cables connect the MUX to appropriate cuffs and transducers placed on the limbs. Lower limbs are raised and placed on an elevated bar or long cushion so that the technician does not have to keep the legs elevated while adjusting the cuffs. An ultrasonic coupling medium is placed on the transducer to insure adequate coupling. The arm cuffs and transducers are applied to the transducer over the brachial artery. The popliteal transducer is fastened over the fossa with surgical tape. A special cuff which uniformly compresses the lower limb is then used. Although not necessary for routine clinical use, approximately five readings were taken on each limb and the readings recorded together with height, weight, age, and sex. A full multitesting as well as medical examination of the patient was available. Most electrocardiograms were computer-interpreted in accordance with the Medical Systems Development Laboratory Computer Program criteria.[10,11] Reports of blood pressure-computer ECG association are available from the studies of Hochberg, et al.[6] The associations in this group were similar to those reported previously.[6,12]

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Instrumentation

Methods based on Korotkoff sounds for popliteal BP are often not convenient or accurate. The literature shows a variety of results, and experience shows that sounds are often difficult to hear, especially the diastolic ones. Various cuffs are used with varying BP's compared to arm BP, but an intra-arterial study suggests that femoral or popliteal BP should be approximately equal to brachial.[13]

The ultrasonic Doppler determination of arterial wall motion under a deflating occlusive cuff is a sensitive method of detecting blood pressure. This technique has been described in detail elsewhere.[1-9] The improved sensitivity provides a means for detecting BP in deep arteries, such as the popliteal. A transducer of appropriate focus (6 cm) and a cuff capable of uniform leg compression validated with intra-arterial pressure measurements was used. The instrument is coupled to a multiplexer to allow all four limbs to be measured with the same instrument without removing cables.

The patient is prepared by placing appropriate cuffs and transducers on the limbs and attaching the cables. A cuff-inflating pressure is selected and a "start" button initiates the automatic operation. Repeat cycles may be automatically performed. The system was operated and recordings made by nurses.

Results

A total of 99 subjects were tested. The study population was primarily made up of subjects who came as part of an executive health check program. All of these were actively engaged in administrative work. None had debilitating chronic disease. There were 83 men and 16 women. Seventy-six % were between 40 and 59 years of age (average 47 years.). Weights ranged up to 233 pounds. (average 171 lbs). BP varied from normotensive to hypertensive. Electrocardiograms showed 41 normal, 17 atypical, 12 borderline, 19 abnormal, and 10 unclassified for various reasons. These four categories appear to be reasonable as screening guides.[14] The groups borderline and abnormal category are the equivalent of the questionable category in Hochberg's previous studies.[10] The same ECG-BP associations then noted can again be discerned.

It proved possible to record the BP's in most extremities. In one patient the right arm pressure was unobtainable and in another the left popliteal was unobtainable. The total time per patient for all preparations and 20 BP determinations (20 would not be required for routine clinical work) averages only 10 to 15 minutes. The ABPI requires the setting of one knob to automatically cycle through five BP measurements. The MUX requires the turning of a knob to select the testing limb. The procedure is thus simple to learn and to perform. Bleed-rate/orifice-size variations are automatically made to produce equal bleed rates and compensate for the large leg cuff air mass. Bleed rates conform to American Heart Association specifications.

Table 1 shows the overall BP data obtained. In the initial part of the study only one arm was recorded, and therefore the averages of both arms are not available for all subjects. The

TABLE 1: Blood Pressure (mmHg)

Avg Class	Average of Both Arms			Average of Both Legs			Right Arm			Left Arm			Right Leg			Left Leg		
	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ
Total Pop. (99)	59	126/87	12/9	97	134/88	10/10	95	127/89	11/11	60	125/88	14/10	99	135/88	11/11	97	134/88	11/11
Normal (41)	25	127/88	10/7	40	135/86	10/8	39	127/87	11/7	26	125/88	12/10	41	136/86	11/8	40	134/87	12/10
Atypical (17)	12	128/88	13/12	16	133/89	11/12	17	130/92	12/13	12	129/87	16/12	17	134/90	9/13	16	133/89	12/11
Borderline (12)	9	120/87	11/9	12	131/89	10/12	11	123/88	10/10	9	118/88	15/9	12	131/90	10/11	12	131/88	10/13
Abnormal (19)	7	121/81	9/7	19	134/89	9/12	19	128/88	11/12	7	121/83	11/7	19	135/90	10/12	19	133/88	9/13
Unclassified (10)																		

N = number of measures available

$\bar{x}$ = average

σ = standard deviation

Borderline to abnormal are the equivalent of "questionable" and normal and atypical of "normal" in the previous Hochberg et al study (10).

average leg pressures are 5-13 mm Hg higher than average systolic arm pressures, whereas the diastolics are closely approximated. The standard deviation of arm and leg pressures is similar, as are the measurements from opposite limbs.

The differences between limbs are shown in table 2. Opposite arms and opposite legs are typically within about 1 mm Hg in systolic and diastolic. The standard deviation of the differences is less (7–8.3 mm Hg) for diastolic than systolic (9.5 to 11.2 mm Hg). The leg shows a higher systolic pressure (6.9, 7.7 mm Hg) than the arm, but the diastolics are almost equal. Standard deviations of the difference are higher for systolic (12.4, 13.3 mm Hg) than diastolic (7, 8 mm Hg). These leg data are compatible with intra-arterial studies showing similar pressures in arms and legs.[18]

TABLE 2: Limb Blood Pressure Differences

		Systolic		Diastolic	
	N	$\bar{x}\Delta$ mmHg	$\sigma\Delta$ mmHg	$\bar{x}\Delta$ mmHg	$\sigma\Delta$ mmHg
Right arm-Left arm	59	1.0	11.2	–1.1	8.3
Right leg-Left leg	97	1.5	9.5	–0.5	7.0
Right leg-Right arm	95	7.7	12.4	–0.5	7.0
Left leg-Left arm	59	6.9	13.3	–0.4	8.0

N = number of comparisons (Note: data not available for correlations on all subjects or all data points)

$\bar{x}\Delta$ = average differences

$\sigma\Delta$ = standard deviation of the difference

Discussion

In any clinic striving to detect significant disease, blood pressure is one of the most common and effective physiological measures used. Yet errors occur. The extension of BP measurements from one arm to all four limbs reduces the chance of technician error. Certainly hypertension is better documented. The extension of the use of BP to diagnosis of obstructive arterial disease is a third significant advantage.

While much peripheral vascular diagnosis can be made on pedal and tibial pulses, much effort (including computer programming) has been expended to analyze distal pulses,[15] but a larger amount of arterial obstruction resulting in symptomatic peripheral vascular disease lies above the popliteal artery.[16] Popliteal artery measurements by occlusive cuff techniques offer potential greater accuracy over tibial measurements because the limb may be uniformly compressed by special cuffs.

The sequential data show the arms should compare within about ±11 mm Hg systolic and ±8 mm Hg diastolic. The legs show a typical systolic difference of ±13 mm Hg, and the diastolics agree within ±8 mm Hg. The results represent the typical of 5 readings. The variation seen may in part be due to respiratory variation. The average difference between arm and leg was 7.7 mm Hg (±13.3) in systolic and 0.4 mm Hg (±8) in diastolic.

Felix et al[9] studied 57 high-school football players and found the differences between the arms was ±9.7 mm Hg systolic, and ±10.3 mm Hg diastolic. The left arm was usually higher. They also studied popliteal and brachial pressures in 34 high school football players and showed that the mean difference between the pressure in the legs was ±14.7 systolic and ±15.1 mm Hg diastolic. Differences between arm and leg pressures showed popliteal higher than brachial by 6.8 ± 12.8 mm Hg systolic and 2.1 ± 9.3 mm Hg diastolic.

Comparison of this and the Felix study suggests that normal young males do not differ in arm-leg pressure from middle-aged executives.

The exact cut-off for abnormal values and differences is not yet defined. Strandness[16] states that a leg systolic BP of 30 mm Hg below brachial should be considered significant. These data show this to be more than two standard deviations. Continued experience with multi-limb measurements with accurate reproducible instruments should clarify and sharpen the criteria for abnormality.

The number of persons reviewed is not sufficient to establish judgments between the data and clinical relationships. However, we have a possible indication of the sensitivity of blood pressure difference values through review of physician diagnosis in 18 that had arm–leg, arm–arm, or leg–leg differences which exceeded the usual ranges previously noted. The physicans' diagnoses are shown in table 3.

Reproducible blood pressures may be conveniently determined in all four limbs with an automatic ultrasonic instrument. Typically the systolic popliteal pressure is about 7 mm Hg greater than in the arm, while the diastolic is similar. Comparison of blood pressures between arms (brachial artery) and legs (popliteal artery)

TABLE 3: Positive Physician Diagnosis* in Subjects with Disparate Blood Pressure Values

Subject	Neuro-Muscular-Skeletal	Thyroid	Pulmonary	Cardiovascular	G.I.	Obese
1		x		x	x	
2					x	
3			x	x		
4		x		x		
5				x		x
6	x (arthritis)	x		x		x
7*	Unavailable					
8*	Unavailable					
9	x (sports injury-disk)					
10						
11	Normal findings		x	x		
12	x (sports injury)		x			x
13				x		
14	x (arthritis)			x		
15						
16	x (disk)					
17	Normal findings					
18	x (sports injury)					
Total	6	3	3	8	2	3

*Diagnosis made by physician without prior knowledge of blood pressure value differences

show similarities which may be helpful in defining cut-off points of normality. The measurement of blood pressure in all four limbs in health-testing opens the possibility of earlier detection of disease.

Summary

Recording of blood pressure from all four limbs in health testing offers the potential of screening for obstructive arterial disease. Recently developed ultrasonic instruments make possible accurate, reproducible, automatic blood pressure measurements of brachial and popliteal arteries. The feasibility and practicality of the instrument was demonstrated on a series of 99 persons. This group of predominantly middle-aged "executive category" males showed ease of P.B. recording in all limbs as a routine nursing or paramedical procedure. The average difference between arm and leg was 7.7 mm Hg (±13.3) in systolic and 0.4 mm Hg (±8) in diastolic. The study allows development of hypothesis regarding data bases that may aid understanding of peripheral pressures.

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book REVIEWS

Radiologic Examination of the Urinary Tract. HOWARD M. POLLACK, M.D. Price, $8.50. Pp. 164 with illustrations. Hagerstown, Maryland: Harper & Row, 1972.

This monograph is extracted from Karafin and Kendall's Urology, Vol. I, in Practice of Surgery. It is published in hard back by Harper and Row. It totals 180 pages. It is the author's stated purpose to ease the transition from naivete to discernment by providing under one cover those basic features of anatomy, physiology and radiology necessary for a rational understanding of uroradiology. In the opinion of this reviewer, the author accomplishes this purpose with admirable clarity and brevity. This book is recommended as required reading by all first year radiology and urology residents. Re-reading immediately prior to specialty board examination would be rewarding. Ample space is given to types of procedures, technique, indications and contra-indications. There is minimal discussion of the radiographic aspects of specific disease processes. Such studies of the abnormal are already covered in many excellent text books and atlases. There is a list of 34 references which is a "key" to the literature, along with a comprehensive index.

MARTIN A. THOMAS, M.D., F.A.C.R.

Progress in Clinical Pathology, Vol. IV. MARIO STEFANINI, Editor. Price, $24.75. Pp. 340 with illustrations. New York: Grune & Stratton, 1972.

The fourth in a series of selected monographs, continues to demonstrate a commendable degree of diversity with respect to both the depth and breadth of the subjects reviewed. It would be unfortunate should the title restrict potential readers to practicing pathologists, however, as several of the monographs are primarily directed toward the practice of clinical/diagnostic and therapeutic medicine. Physicians in all fields will find a wealth of current information in several of these monographs.

Two chapters deal with the complex subjects of Endocrine Profiles and Acid/Base, electrolyte profiles. Both are complete, heavily referenced reviews, yet are presented in a concise, organized and understandable fashion. The first details each endocrine gland, the hormones produced and the clinical laboratory tests best suited to their evaluation. Many common and some not so common interrelationships are discussed. The chapter on Acid Base balance, although seemingly complicated in the beginning, explores the use of normograms to aid in rapid evaluation and selection of appropriate therapy.

The chapter on Laboratory Recognition of CCoronary Artery Disease quickly and clearly reviews this interesting and popular subject. Although the author's classification of Hyperlipoproteinemias is not completely up to date, this mongraph still reflects what should be, but is not, common knowledge in the medical community.

For those with academic leanings, the editor has included a chapter on Radio-immuno Assays and another entitled Selected Topics in Immunology. The first explores the complexities of reagent preparation and test performance within the scope of basic chemistry and immunology. The reader is left with a better understanding and appreciation of this subject. The topics in immunology reviews the exciting relationships between the Epstein-Barr Virus, Infectious Mononucleosis and Burkitts Lymphoma. In addition, hepatitis and the HB antigen are discussed.

A chapter on Control of Hospital Associated Infection reviews this current but sometimes not so popular problem. As an established leader in the field, the author details the organization, mechanics and implementation of his programs; which remain the standard by which others are judged.

The chapter on Reagent Kits is most definitely not "for pathologists only." The problems of testing and controlling the quality of the reagent kits is discussed. It should be required reading for all physicians who find it necessary to perform their own laboratory tests and serves as a firm reminder that many short cuts and gimmicks have no place in quality medical care.

Finally, a chapter on Veterinary Pathology is included and will surprise most readers with its multitude of interesting facts. Emphasis is placed on areas where clinical laboratory medicine is being used to diagnose and treat diseases in the animal population.

Over the years the periodic publication of books of this nature had tended to increase. In seeking to compile and condense the vast and ever expanding volume of information appearing in our medical and scientific journals, they achieve their goal. To the busy physician, Progress in Clinical Pathology IV serves well as a convenient and reliable form of continuing education.

WALTER E. LAWRINSON, M.D.

The Pathogenesis of Atherosclerosis. ROBERT W. WISSLER AND JACK C. GEER, Editors. Price, $23.00. Pp. 262. Baltimore: The Williams & Wilkins Company, 1972.

The United States is in the midst of an epidemic of atherosclerosis. This small volume is an attempt to describe, in molecular, anatomical and epidemiologic terms, the reasons for that epidemic, to delineate what can be done about it on the basis of present knowledge, and to point out some possible pathways to more definitve solutions. The book is a monograph which resulted from a symposium held by the American Association of Pathologists and Bacteriologists. As is true of most books written by a number of contributors, the content and quality of the writing is spotty, ranging from a poor chapter on animal models in atherosclerosis to an excellent chapter on risk factors by Dr. Jeremiah Stamler. The advantage of such a multi-authored monograph, on the other hand, is that it can be read selectively without missing vital information. While few physicians can practice medicine without dealing with some aspect of atherosclerosis (including pediatricians, who should be at the forefront of prevention), few are likely to be absorbed enough in the problem to want to read all of these reviews in detail. The chapters on animal models, the arterial smooth muscle cell, and mechanical stress in arteries, for example, may be of more interest to pathologists, while those on risk factors, thrombosis and hyperlipoproteinemia will be of more immediate interest to internists.

While much of the material presented is familiar in one form or another to most physicians, some of the conclusions to which currently available data points are surprising. That diet, hyperlipemia, diabetes, smoking and hypertension are important in the development of atherosclerosis is reasonably well-accepted. That obesity and sedentary living, per se, when not accompanied by other risk factors, may not be of primary importance is less well appreciated (and perhaps not yet conclusively demonstrated). That hypercholesterolemia may be the sine qua non of atherosclerosis is perhaps difficult for many physicians to accept, but this conclusion appears to be supported by a wealth of available data. In this regard, Stamler's chapter on risk factors is particularly important because his review of the available literature is exhaustive and, while his zeal leads him sometimes to editorialize, the data are there for the reader to examine critically for himself. This chapter is useful, moreover, in its attempt to analyze risk factors independent of one another and because of the wealth of data which Stamler brings to bear in burying for once and for all the concept that dietary manipulation is ineffective in the control of plasma cholesterol (a concept which is still being taught in some medical schools).

Practically swept away in this oily tide, but of very real merit, is the chapter on thrombosis. The role which abnormal coagulation may play is of great importance, not only in the acute catastrophes associated with advanced atherosclerosis but also in the development of early atheromas. It is an area likely to receive more attention as our understanding of atherogenesis increases.

This small book, then, is an excellent review of a complex and timely subject. It deserves perusal by most physicians, selective reading by those physicians whose practices are heavily laden with atherosclerotic patients, and careful and complete study by all researchers in fields relating to atherogenesis.

JOHN C. LAROSA, M.D.

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medical annals of the district of columbia

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The Psychoanalytic Study of Society. WARNER MUENSTERBERGER AND AARON ESMAN, Editors, Price, $12.00. Pp. 258. New York: International University Press, 1972.

This collection of articles by a number of authors continues a series in which extensions and ramifications of psychoanalytic knowledge are presented. At times, psychoanalytic concepts have been invoked to provide scientific rationalization for an essentially personal point of view. In this reviewer's opinion this is true of the contribution, "The Day of a Psychoanalyst at Woodstock" by James L. Titchener. In contrast there is David Zern's careful and double-shafted approach toward evaluating the validity of a particular psychoanalytic concept in differing societies. As we have learned to be cautious in extrapolating from animals to humans in medicine, so is caution necessary in applying psychoanalytic concepts to society without the development of sufficient data. Wolfenstein presents an example of a careful extension of psychoanalytic knowledge—in this instance into the field of psychobiography. Dale Meers' poignant description of the Black unwed mother in our Washington ghetto raises provocative questions about welfare policy and the ineffectiveness of many of our social systems as applied to the ghetto. Bryce and Ruth Boyer demonstrate the Apache Indian's continuing stimulation of aggression in their child rearing practices at a time when few sanctioned outlets are available, what with the settling in to reservation life. As a consequence, these Indians turn their aggressions onto themselves in a tragic and self-destructive manner. In this day of wonderment about health delivery systems, it would be fascinating to apply Pouillon's anthropological concept of the therapeutic triangle—doctor, patient, and disease treated—to determine if new insights might emerge. There are other articles on art and personality, on the integration of sin vis-a-vis personality and society in Tahiti, on the development of myths and on Black Bart, the California highwayman, and more to attract the reader who is interested in the various applications of psychoanalysis to circumstances beyond the immediate clinical domain.

BERNARD MATHIS MALLOY, M.D.

Emergency Room Diary. THEODORE ISAAC RUBIN, M.D. Price, $6.95. Pp. 193. New York: Grosset & Dunlap, 1972.

Theodore Isaac Rubin was, contrary to his twenty years later assessment, a truly sophisticated intern in a southern California community hospital emergency room. His diary of his E.R. rotation reflects not only the agony of an extremely fatigued intern working thirty hours a day and beseiged with myriads of non-acute patients (the very sick stand out in vivid detail), but a mature, young doctor with the supreme capacity for empathy and introspection.

This chronicle is not for the weak of heart and the unfeeling: too often the savagery of a real world comes out to the reader to shock and astound. For the non-medical readers, the use of medical jargon, despite glossary, will only serve to barricade full understanding of the rapid tempo and soul of a busy emergency room. For everyone else, this book should prove a delight.

RAYMON A. NOBLE, M.D.

Surgical Pediatrics. STEPHEN L. GANS, M.D., Editor. Price $19.50. Pp. 337 with illustrations. New York: Grune & Stratton, 1972.

The past two decades have seen a crescendoing interest in pediatric surgery and an increasing number of volumes dealing with its technical aspects. It is refreshing to read this book, "Surgical Pediatrics," edited by Stephen L. Gans, M.D., which deals exclusively with the non-technical aspects of the care of infants and children with surgical illnesses. This is the first such American publication of which I am aware. The author has called upon 22 consultants who have written on such important topics as anesthetic management of infants and children; methods of dealing with families of critically ill or dying children; the genetic background of many of the congenital illnesses; supportive care of children, including fluid electrolyte maintenance, hematologic disorders and use of blood components; physiologic monitoring; and infectious disease management.

While the book is intended primarily for pediatric surgeons, it is an excellent reference for all surgeons dealing with the surgical problems of infancy and childhood.

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Indications: Santyl Ointment is indicated for debriding dermal ulcers and severely burned areas. In other types of necrotic skin lesions reports on the use of Santyl Ointment have been limited to clinical observations without controls.

Contraindications: Application is contraindicated in patients who have shown local or systemic hypersensitivity to Collagenase.

Precautions: The enzyme's optimal pH range is 7 to 8. Lower pH conditions have a definite adverse effect on the enzyme's activity, and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene and heavy metal ions such as mercury and silver which are used in some antiseptics. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before Santyl Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's solution do not interfere with the activity of the enzyme.

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin.

A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by protecting the healthy skin with a material such as Lassar's paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although none has been observed to date.

Adverse Reactions: Adverse reactions to Collagenase have not been noted when used as directed.

Dosage & Administration: Santyl Ointment should be applied once daily (or once every other day in the case of outpatients) in the following manner.

(1) Prior to application the lesions should be gently cleansed with a gauze pad saturated in normal saline, buffer (pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.

(2) Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odor, it is desirable to use an appropriate topical antibacterial agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with Santyl Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of Santyl Ointment. Should the infection not respond, therapy with Santyl Ointment should be discontinued until remission of the infection.

(3) Santyl Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds, or, when dealing with shallow wounds, to a sterile gauze pad which is then applied to wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

(4) Crosshatching thick eschar with a #11 blade is helpful. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

(5) All excess ointment should be removed each time dressing is changed.

(6) Use of the ointment should be terminated when sufficient debridement of necrotic tissue has taken place.

Overdose: Action of the enzyme may be stopped, should this be desired, by the application of Burow's solution U.S.P. (pH 3.6-4.4) to the lesion.

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Varma A O et al: *Surg. Gynec. Obstet. 136*:281, Feb. 1973.

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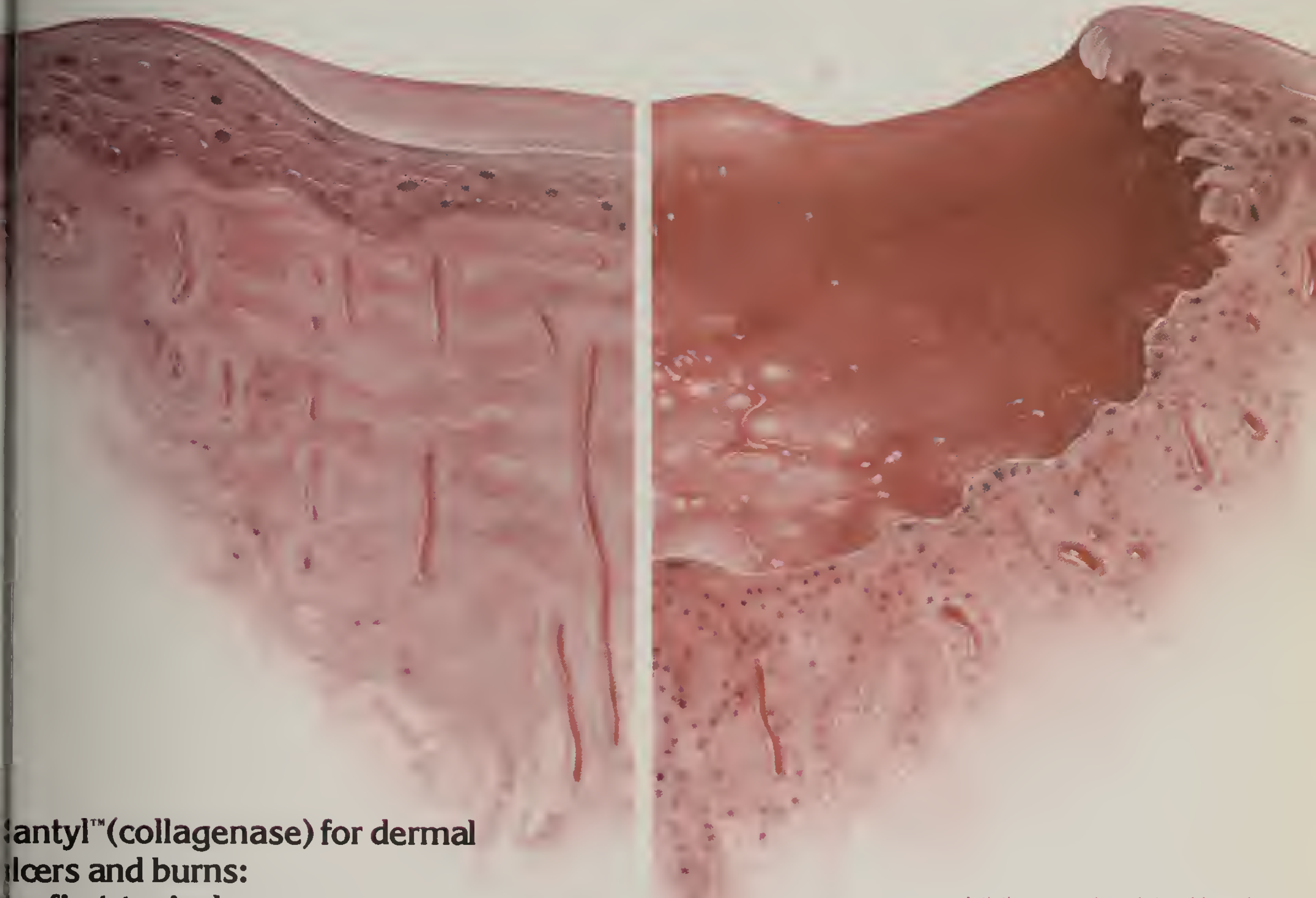

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References: **1.** Olsen, J.R.: Journal-Lancet *85*:287 (July) 1965. **2.** Giorlando, S.W.: Ob/Gyn Dig. *13*:32 (Sept.) 1971. **3.** Decker, A.: Case Reports on File, Medical Department, Julius Schmid. **4.** Giorlando, S.W., Torres, J.F., and Muscillo, G.: Am. J. Obst. & Gynec. *90*: 370 (Oct. 1) 1964. **5.** Lechevalier, H.: Antibiotics Annual 1959-1960. New York, Antibiotica Inc., 1960. pp. 614-618. **6.** Friedel, H.J.: Maryland M.J., *15*:36 (Feb.) 1966.

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There are particularly good chapters on the interpersonal relationship between surgeon, child and family and also the interrelationship of surgeon with the family of a dying or critically ill child, written by C. Everett Koop, Chief of Pediatric Surgery at the Children's Hospital of Philadelphia. Genetic counseling of families whose children are born with genetically-controlled anomalies is covered well by Miriam G. Wilson, M.D., Chief, Genetics Division at the Los Angeles County-USC Medical Center. Both of these are excellent chapters well worth reading by both pediatric surgeons and others dealing with anomalies and diseases of children. Dr. Robert M. Smith has contributed two chapters on the anesthetic management of children and infants, an area in which he has achieved world renown as Anesthesiologist-in-Chief of the Boston Children's Hospital.

Drs. Filler, Eraklis and Das of Boston have contributed an excellent chapter on fluid and electrolyte management of the infant, along with total parenteral hyperalimentation. They are perhaps the foremost authorities in the United States on total parenteral alimentation of infants. An excellent chapter on physiologic monitoring of the surgical infant is written by Marc I. Rowe, M.D., Chief of Pediatric Surgery at the University of Miami, whose studies of the physiology of the neonate over the past decade have contributed to the increasing skill and success with which surgical neonates have been managed.

Two excellent chapters on the preoperative hematologic evaluation of the child and the use of whole blood and blood components in pediatric surgery are sophisticated views worthy of reading by all dealing with surgical problems in children. A chapter on antibiotic therapy by Benjamin Kagan, M.D. of Los Angeles is also an excellent review.

There is some repetition in this book, of necessity, but the editor has kept it to a minimum. Some of the concepts advanced are slightly at variance with generally accepted procedures in the Washington area, but are honestly stated by the authors and are certainly equally valid approaches. The book perhaps could have been much stronger had there been a section on the neonate, particularly the premature neonate, written by an established neonatologist. Furthermore, one of the areas of pediatric surgery evoking increasing interest is the preoperative management of the child coming in for elective surgery and the general care of children in hospitals. This topic might have been covered better by a child psychiatrist. Since the spectrum of surgical illnesses in children seems to follow the incidence of viral illnesses in the community, I believe the volume could have been enhanced by a chapter on the interrelationship of viral illnesses and surgical illnesses, such as intussusception and appendicitis. Also, a chapter on the development of immunocompetence in the child and its relation to surgical illnesses might well have been included.

This volume is very readable and well worth the attention of all surgeons and surgical specialists dealing with children.

RICHARD M. SCHISGALL, M.D.

Artificial Organs and Cardiopulmonary Support Systems. FELIX T. RAPAPORT AND JOHN P. MERRILL, Editors. Price, $15.00. Pp. 186 with illustrations. New York: Grune & Stratton, 1972.

This collection of essays previously published in other journals in scientific detail, summarizes the current status of artificial organs and other substitutes for permanent allografts. The presently available technology is evaluated and future progress is outlined for primarily medical students.

Early dialysis for chronic kidney failure, utilizing preferably an arteriovenous shunt as method of access to the dialysis apparatus is the treatment of choice. For economic reasons home dialysis is preferable to center dialysis. HL-A identical transplantation is warranted without previous dialysis. Cadaver organ transplantation should be the ultimate goal for renal allografting. If the allograft fails rather than excessively vigorous immunosuppressive therapy, the kidney should be removed and the patient returned to the dialysis program. For acute renal failure, peritoneal dialysis is the treatment of choice, unless a contra-indication exists.

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"Probably" effective: For the treatment of vulvovaginal candidiasis.

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Precautions: Cases of sensitization and irritation have been reported. When noted the drug should be discontinued.

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ECG Problems

(from page 233)

INTERPRETATION:
1. First degree A-V block.
2. Left ventricular hypertrophy.
3. Left axis shift.

The heart rate is 65 per minute, atrial and ventricular, with PR interval 0.30, QRS interval 0.09, and electrical axis -45°. The PR interval identifies first degree A-V block.

Left ventricular hypertrophy is diagnosed by applying any of several sets of criteria. The most generally accepted criteria currently are those of Estes, consisting of a point scoring system as follows:

1. QRS amplitude (R or S over 20 mm. in a limb lead or S, V_1, V_2, or V_3 or R, V_4, V_5 or V_6 greater than 25 mm.): 3 points.
2. ST segment opposite in direction to the QRS: 3 points. (If on digitalis: 1 point)
3. Axis–More left than -15°: 2 points.
4. QRS duration over 0.09 seconds: 1 point.
5. Ventricular activation time greater than 0.04 seconds: 1 point.

Five or more points indicates left ventricular hypertrophy. Four points indicates probable LVH.

This patient has eight points, demonstrating all the abnormalities, but losing two points because he was receiving digitalis (the probable cause of his first degree A–V block).

Edited by Robert R. Montgomery, M.D.

oxygenators and artificial kidneys, the factor limiting transfer of solute was not the membrane itself, but the blood boundary level, that is the slower moving layer of blood next to the membrane. The concept of the membrane oxygenator for acute self-limited pulmonary disease was applied with modest success, permanently implantable mechanical lungs are a dream of the future.

Thromboembolism, disseminated intravascular coagulation and inadequate cardiac output are some of the problems of construction of an artificial heart. In regard to the intra-aortic cardiac counterpulsation balloon pump, the indication must be lack of response to medical therapy. If no improvement by either results, coronary angiography and direct coronary revascularization may be considered. A hydrolic system encasing both lower extremities, exerting positive and negative pressure, Soroff claims, effects venous return to the heart and normal cardiac output. In the reviewer's judgment, it must be demonstrated, whether patients with various forms of cardiac support survive because of or in spite of such mechanical devices.

Intravenous infusion of a total nutrient solution in patients with absent or nonfunctional small bowel proved temporary success. Twenty per cent glucose, balanced electrolytes and a protein source of mixtures of purified levo-amino acids improved growth, healing and regrowth of partially resected organs. Infusing the nutrient solution into the venous side of a surgical arteriovenous fistula is an attractive technique.

The section on treatment of liver failure discusses the utilization of baboon, pig and human liver explants, cross-circulation with baboons or humans and exchange transfusion. Maintenance of patients with such devices is even more difficult than predicting which patients would recover and which would not. Hepatic coma has an inherently unpredictable course.

Methods of resurfacing denuded skin areas were described. The problems to be attacked are infection and fluid loss due to evaporation. Fresh healthy skin allografts appear the optimal coverage and no synthetic material is available as an adequate substitute.

Kidneys perfused on a suitable machine with plasma under hypothermic conditions, allowing the observer to essay their function may have advantages over simple cold storage. Organ freezing with the exception of skin and sperm has not yet progressed to a practical stage. An intermediary animal recipient, whose immune system was destroyed, can maintain an organ for a number of days in experiments.

With the exception of the renal dialysis machine, there is no adequate substitute for normal organ function. The symposium which the reviewer doubts needed publication, outlines research into technology, directed at the end results of diseases, rather than at the underlying mechanisms of their development. The elaborate technology will then be set aside and the book reviewed will become another frustrating episode of medical technological history and outdated as the Drinker respirator for poliomyelitis.

KAREL B. ABSOLON, M.D., PH.D.

Lipids, Malnutrition and the Developing Brain. A Ciba Foundation Symposium. Price, $14.50. Pp. 326 with illustrations. Amsterdam: Associated Science Publishers, 1972.

Peptide Transport in Bacteria and Mammalian Gut. A Ciba Foundation Symposium. Price, $7.25. Pp. 161 with illustrations. Amsterdam: Associated Science Publishers, 1972.

These two books are not what a physician would orinarily read. On the other hand, the basic material is of great importance for all physicians. The two volumes represent papers and discussions of forty-five internationally known scientists and physicians meeting in London over a four day period at two separate Ciba Foundation Symposia. Such a meeting of biochemists, physiologists, neurologists, gastroenterologists and others in a large gathering can be very fruitful in the proper computation of knowledge.

The book *LIPIDS, MALNUTRITION & THE DEVELOPING BRAIN* represents the formulations of the papers and discussions of the three day meeting in London, October 19th-21st, 1971. The symposium emphasized that wherever malnutrition prevails, children are always the most severely affected, and that growth is not only retarded but even stunted. Studies on protein-calorie malnutrition have been covered in other symposia over the years, but this particular symposium dealt only with lipid metabolism and especially with the essential fatty acids, linoleic and linolenic. The conclusion of the symposium was that in the absence of these essential fatty acids, there was profound functional disturbance in the developing brain, especially in the premyelination phase, mitochondrial pathway and glial multiplication, with resultant damage to structure and function, and irreversibility. There was no mention by any of the contributors of a possible relationship between the popular low fat-low cholesterol diet and brain development, since this type of diet might lead to essential fatty acid deficiency.

The book *PEPTIDE TRANSPORT IN BACTERIA AND MAMMALIAN GUT* represents the formulations of a one day symposium in London on November 11, 1971 (not 1972 as noted in the preface). The entire symposium concerns itself with the comparison of absorption and breakdown of peptides in mammalian gut and in bacteria, since bacteria can obtain amino acids from peptides taken into the cell from the external environment, and there is evidence that the same process may occur in the small intestine of mammals. There seems to be some correlation between amino acids deficiency and hereditary diseases, and it is important for the modern physician to keep in mind that some common drugs can interfere with intestinal transport enzymes. This certainly must be kept in mind where continuous use of a drug is essential for management of an illness, such as antibiotics in rheumatic heart disease, or tranquilizers in anxiety.

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OBITUARIES

Daniel L. Seckinger, M.D.
1893–1973

Dr. Daniel L. Seckinger, public health director of the District of Columbia from 1949 to 1957, died February 22, 1973. He resided at 921 Spanish Circle, Delray Beach, Florida.

Born in Rincon, Georgia, he received a B.A. degree from Lenoir-Rhyne College in Hickory, North Carolina, a master's degree from the University of North Carolina and his M.D. degree from the Johns Hopkins University School of Medicine. He also held a master's degree and a doctorate from the Johns Hopkins University School of Hygiene and Public Health, where he specialized in epidemiology and virology. He interned at the Johns Hopkins Hospital and served residencies at St. Mary's Hospital and the Pierre Clinic in Pierre, South Dakota.

He later organized the Bureau of Preventable Diseases for the Rockefeller Foundation and the Georgia Board of Health. After serving as director of preventable diseases for the Georgia State Board of Health in Atlanta, he came to Washington, D.C., where he was assistant health officer until 1949. He had also served as coordinator of health and hospitals and acting superintendent of the old Gallinger Hospital, which is now D.C. General Hospital.

Dr. Seckinger assumed his position as D.C. public health director on November 3, 1949. During his nearly 18 years there, he made a considerable contribution to improving health services, devoting his energies to such problems as wiping out tuberculosis here, lowering the infant mortality rate and improving and increasing hospital facilities. He also pioneered in establishing the first public health clinic for alcoholics in the nation and led in the establishment of a venereal disease control program.

A life member of the Medical Society of the District of Columbia, Dr. Seckinger was a former president of the Metropolitan Health Officers Association and a member of the American Medical Association as well as the Johns Hopkins Medical-Surgical Association. He had also been a member of the Southern Medical Association and was a fellow of the American Public Health Association.

He is survived by his wife, June W., of the home; a son, Dr. Daniel L., Jr., of Miami, and two grandsons.

James M. Clements, M.D.
1928–1973

Dr. James M. Clements, a Washington area surgeon, died February 2, 1973. He resided at 4420 Faraday Place, N.W.

Born in Indiana County, Pennsylvania, he received his undergraduate and M.D. degrees from Georgetown University here. He served his internship at D.C. General Hospital, and residencies at Georgetown University and the old Mt. Alto Veterans Administration hospitals. He had been an assistant professor of surgery at Georgetown University School of Medicine, and was engaged in the private practice of General Surgery at the Forest Glen Medical Center in Silver Spring, Maryland.

Dr. Clements was an Active member of the Medical Society of the District of Columbia.

He is survived by his wife, Marie; two daughters, Margherite and Christine; and three sons, Vincent P., James M., Jr. and Paul A.; four brothers, John W., Rocco F. and Edward J., of Washington, and Peter, of Pennsylvania, and three sisters, Phyllis and Mary Clements and Rose Harner of Washington.

John Ronald Day, Jr., M.D.
1934–1973

Dr. J. Ronald Day, Jr., who practiced Obstetrics and Gynecology in the Washington area, died January 23, 1973. He resided at 4010 Underwood Street, Chevy Chase, Maryland.

A native of Annapolis, Maryland, Dr. Day was a graduate of the University of Maryland. He received his M.D. degree from the George Washington University School of Medicine here, and he also served his internship and residency at the George Washington University Hospital. He was engaged in the private practice of Obstetrics and Gynecology at the Bethesda North Medical Building in Rockville, Maryland.

An Active member of the Medical Society of the District of Columbia, Dr. Day had also been a Junior Fellow of the American College of Obstetrics and Gynecology, a Junior member of the American Society for the Study of Sterility and a member of the William Beaumont Society.

He is survived by his wife, Loretta Newby Day, and two daughters, Lisa and Marcella, all of the home.

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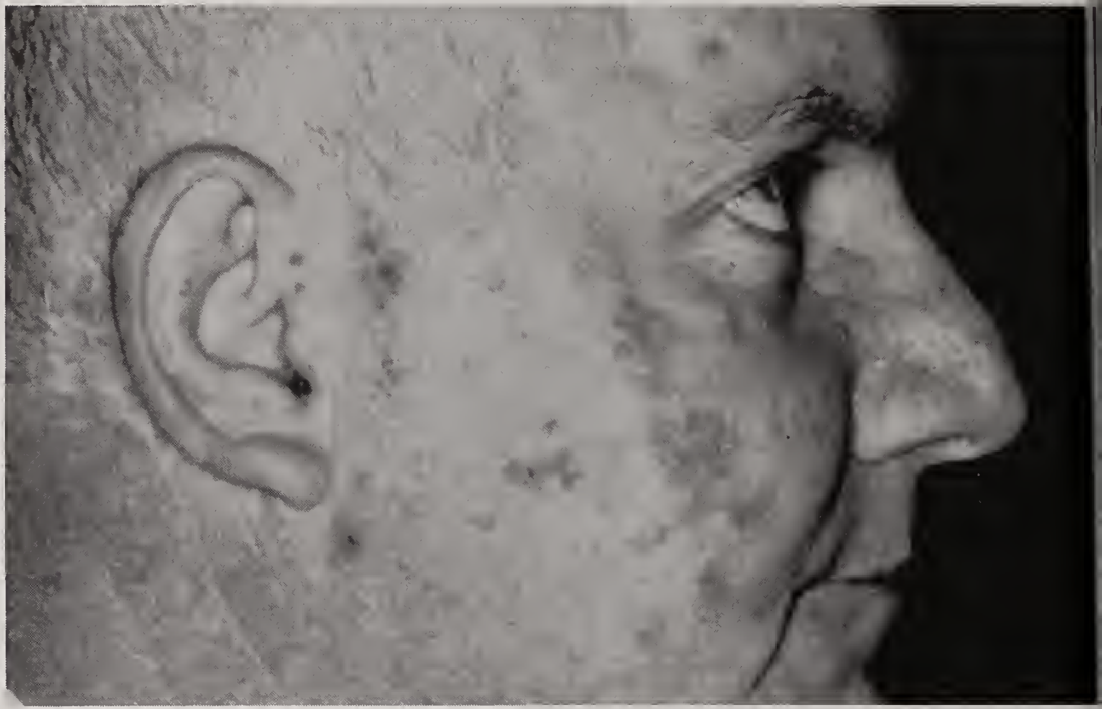
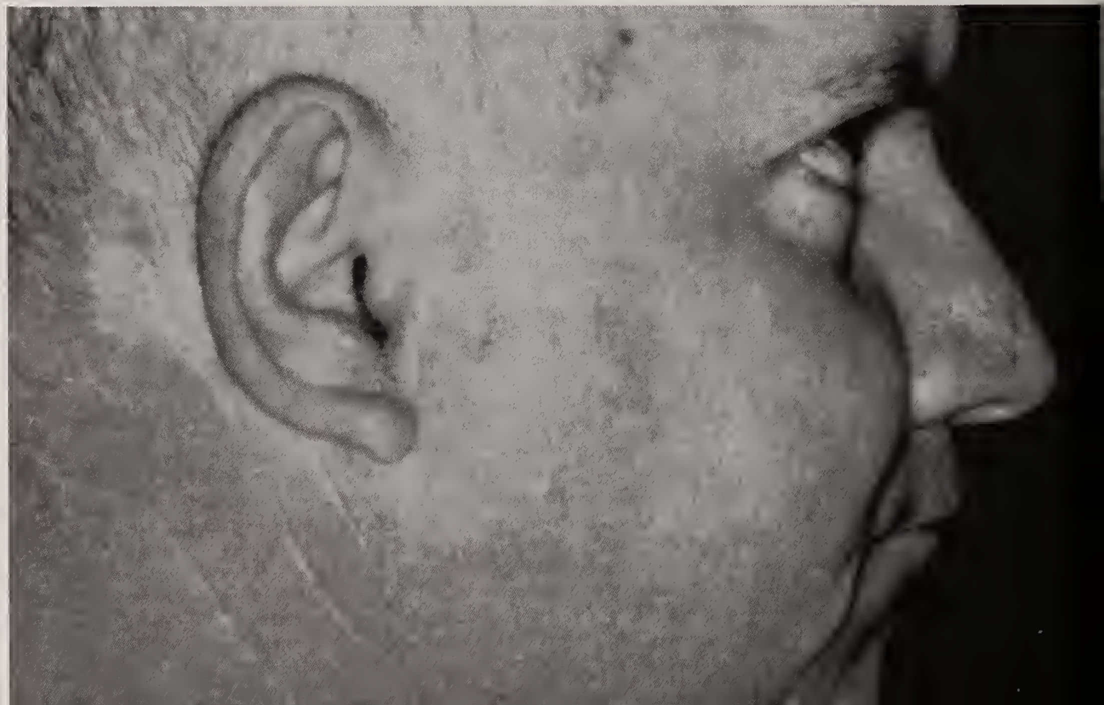
Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.



Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.



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Gilbert H. Mankin, M.D.
1892–1972

Dr. Gilbert H. Mankin, a retired Washington area physician, died September 4, 1972. He resided in Phoenix, Arizona.

Born in West Virginia, he received his undergraduate and M.D. degrees from Cornell University in New York. He interned at the U.S. Naval Hospital here and served an internship and residency at Johns Hopkins Hospital. He had been an Instructor in Otolaryngology at Georgetown University School of Medicine and had maintained a private practice of Otolaryngology until his retirement in 1961.

Dr. Mankin was a Life member of the Medical Society of the District of Columbia, and had also been a member of the American Medical Association and the Association of Military Surgeons.

James P. Leake, M.D.
1881–1973

Dr. James P. Leake, a Washington area physician, died February 21, 1973. He resided at 2733 Ontario Road, N.W.

Born in Sedalia, Missouri, he received his B.A. and M.D. degrees from Harvard University. He served his internship and residency in Boston area hospitals before coming to the Washington area in 1913 to practice General Medicine.

An Associate member of the Medical Society of the District of Columbia, Dr. Leake had also been a member of the Association of Military Surgeons and the American Public Health Association. He was also a Fellow of the American Medical Association and the New York Academy of Medicine.

He is survived by three daughters, Mrs. Alice L. Lawless, Mrs. Mary L. Craven and Mrs. Elizabeth L. Quinn, and twelve grandchildren.

Robert U. Cooper, M.D.
1898–1973

Dr. Robert U. Cooper, a Washington area physician and surgeon, died February 13, 1973. He resided at 3150 Pennsylvania Avenue, S.E.

Born in Selinsgrove, Pennsylvania, he received a bachelor's degree from Springfield College and a master's degree from Clark University. He received his M.D. degree from the University of Michigan. He served his internship and residency at the University of Michigan Hospital, following which he came to Washington, D.C., where he began a private practice in General Surgery in 1927. He had also been on the staffs of Providence and Sibley Memorial hospitals.

Dr. Cooper was also interested in the field of investments, having authored a book, "Investments for Professional People," and had been a featured speaker at a number of professional conferences.

He was one of the founders and directors of the old Anacostia National Bank and had served on the board of advisors of the National Bank of Washington.

A Life member of the Medical Society of the District of Columbia, Dr. Cooper also held membership in the American Medical Association and the Washington Academy of Surgery. He was also a Fellow of the American College of Physicians and of the International College of Surgeons.

He is survived by his wife, Carrye J. Cooper, of the home address; a son, William I., of Guadalajara, Mexico; two daughters, Carrye E. Cooper, of Los Angeles, and Betty Ennis, of Charles Town, West Virginia; a sister, Katherine Morgan, of Williamsport, Pennsylvania, and three grandchildren.

Reaumur S. Donnally, M.D.
1920–1973

Dr. Reaumur S. Donnally, who had practiced Internal Medicine in the Washington area for 24 years, died March 19, 1973. He resided at 1827-23rd Street, N.W.

A native of Washington, he was a graduate of Harvard University and received his M.D. degree from the Johns Hopkins University School of Medicine. He served his internship and residency at Bellevue Hospital in New York City. He had been a consultant in cardiology at the old Emergency and Garfield hospitals, and had also been on the staffs of the Washington

Hospital Center and Doctors, George Washington University, Georgetown University and Sibley Memorial hospitals. He had maintained offices at his home and for the past 15 years had been advisory editor on medicine for the Encyclopedia Americana.

For 20 years Dr. Donnally had been a consultant for the Chesapeake and Potomac Telephone Company, and was an examiner for the New England Mutual, Aetna and Lincoln Life Insurance companies and the Sun Life Assurance Company. Dr. Donnally had also been one of the late President John F. Kennedy's personal physicians, having met him while a student at Harvard.

An Active member of the Medical Society of the District of Columbia, he was also a member of the Johns Hopkins and Louis Mackal medical societies.

Dr. Donnally is survived by his wife, Katherine Ann Donnally, a daughter, Margaret, and a son, Robert, of the home; two other sons, Reaumur S., Jr., and Vincent R., both students at the Virginia Polytechnic Institute; his mother, Bessie Donnally, of Berkeley Springs, West Virginia, and a brother, Harry, of New York, New York.

Robert H. Craft, M.D.
1930–1973

Dr. Robert H. Craft, who practiced General Surgery in the Washington area, died February 13, 1973. He resided at 220 Beaumont Road, Silver Spring, Maryland.

A native of Washington, D.C., Dr. Craft received his undergraduate and M.D. degrees from George Washington University here. He served internships at the Washington Hospital Center and Garfield Memorial Hospital, and his residency at the Washington Hospital Center. He had been engaged in the private practice of General Surgery since 1962, and had also been on the staffs of the Washington Hospital Center, Doctors, Suburban, Children's Prince George's, Holy Cross and Sibley Memorial hospitals.

Dr. Craft was an Associate member of the Medical Society of the District of Columbia.

He is survived by his wife, Claire A. Craft, of the home address.

Timothy F. O'Donovan, M.D.
1923–1973

Dr. Timothy F. O'Donovan, who practiced general medicine in the Washington area for more than 20 years, died February 12, 1973. He resided at 5408 Manchester Drive, Camp Springs, Maryland.

A native of Washington, he received both his undergraduate and M.D. degrees from Georgetown University. He interned at Providence Hospital here, and served residencies in internal medicine at Providence and Georgetown University hospitals. He established a private practice here in 1950. In 1952 he joined the Navy as a medical officer, resuming his practice after two years of active duty. He was also on the staffs of Providence and Cafritz Memorial hospitals.

An Associate member of the Medical Society of the District of Columbia, Dr. O'Donovan also held membership in the American Medical Association, the Prince George's County Medical Society and the Medical and Chirurgical Faculty of the State of Maryland. He was also a Fellow of the American Academy of Family Physicians.

He is survived by his wife, Jean Mackey O'Donovan, and five children, M. Colleen, Meghan Mary, Stephen M., Terrence M. and Sean H., all of the home; another daughter, Maureen O'Donovan Klepper, of Annapolis; two other sons, Timothy F., Jr., of Long Island, New York, and Denis P., of Camp Springs; his mother, Julia M. O'Donovan, of Hillcrest Heights, Maryland; a brother, Jeremiah P., of Silver Spring, Maryland; a sister, Sheila O'Donovan Rogers, of Orange, California, and three grandchildren.

Kline A. Price, M.D.
1907–1973

Dr. Kline A. Price, who practiced Urology in the Washington area for nearly 40 years, died March 9, 1973. He resided at 4031-19th Street, N.E.

A native of Washington, he received both his undergraduate and M.D. degrees from Howard University here and interned at Freedmen's Hospital, entering private practice in 1934. He had been an associate clinical professor of Urology at the Howard University School of Medicine, a position which he held for 36 years. He also published a number of scientific articles during this time.

An Active member of the Medical Society of the District of Columbia, Dr. Price was also a member of the American Medical Association, the National Medical Association and the Medico-Chirurgical Society of the District of Columbia.

He is survived by his wife, Charlotte S. Price, of the home address; two sons, Dr. Kline A., Jr., of Columbia, Maryland, and Hugh B., of New Haven, Connecticut; and seven grandchildren.

Arnold S. Greenberg, M.D.
1918–1973

Dr. Arnold S. Greenberg, an Otolaryngologist who specialized in Allergic Diseases, died March 14, 1973. He resided at 7509 Helmsdale Road, Bethesda, Maryland.

A native of Washington, he received his M.D. degree from the George Washington University School of Medicine. He interned at Providence Hospital and served his residency at Sibley Memorial Hospital. The recipient of a Fellowship in Allergy, he studied under Dr. Townsend B. Friedman at the Children's Memorial Hospital in Chicago.

During World War II he served as a medical officer with the 84th Infantry Division in Europe and was awarded a Purple Heart and the Bronze Star.

A former chief of the Ear, Nose and Throat division of the Washington Hospital Center, Dr. Greenberg was a staff member there and at Children's Hospital here. In 1970 he received the Vicinnial Medal from the Georgetown University School of Medicine, where he had taught for 20 years. He also maintained offices in the District and in Silver Spring, Maryland.

An Active member of the Medical Society of the District of Columbia, Dr. Greenberg also held membership in the American College of Allergists, the American Academy of Allergy, the International Correspondence Club of Allergy, the George Washington University Medical Society and the Montgomery county and Jacoby Medical Societies.

He is survived by his wife, Ruth Rosendorf Greenberg, of the home address; three sons, Richard, of Potomac, Maryland, and Robert and Paul, of Bethesda; his mother, Kitty Greenberg, and a sister, Shirley Bartow, of Washington; and two grandchildren.

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1. GOODMAN, J., ET AL: Bacterial endocarditis as a possible complication of chronic hemodialysis. New Eng. J. Med., 1969, 280, 876.

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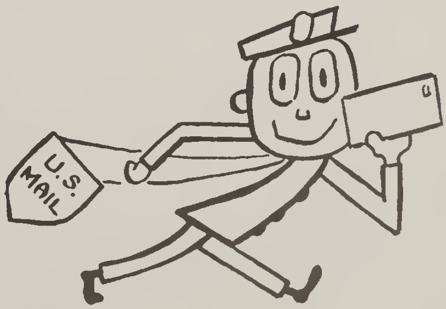

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U.S. Tree Farms System, Inc. 9

Nurse Registries

Association of Undergraduate and
  Practical Nurse Registry T-246
District of Columbia Manpower
  Administration T-241

Nutrition Education

Dairy Council of Greater Metropolitan
  Washington, D.C. T-260

Pharmaceuticals

Burroughs Wellcome & Company 6
Geigy Pharmaceuticals 1
Knoll Pharmaceutical Company T-252
Eli Lilly & Company 10
McNeil Laboratories, Inc. T-250
Ortho Pharmaceutical Corporation T-257
Pharmaceutical Manufacturers Association .4-5
William P. Poythress & Company 7
A. H. Robins Company 11, 12
Roche Laboratories 2-3, T-242–243
Julius Schmid, Inc. T-254–255
G. D. Searle & Company T-248–249
Stuart Pharmaceuticals Division
  of ICI America Inc. T-247
The Upjohn Company 13

Pharmacy

Peoples Drug Stores T-239

Real Estate

Shannon & Luchs T-244

Vacation and Recreation

Sheraton Inn—Ocean City T-238

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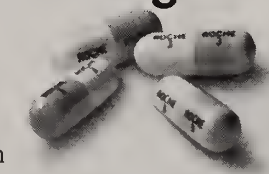

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Contraindications: Patients with know
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combined effects with alcohol and other CNS
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patients against hazardous occupations requiri
complete mental alertness (*e.g.*, operating mac
ery, driving). Though physical and psychologi
dependence have rarely been reported on reco
mended doses, use caution in administering to
addiction-prone individuals or those who mig
increase dosage; withdrawal symptoms (inclu
convulsions), following discontinuation of the
drug and similar to those seen with batbiturat
have been reported. Use of any drug in pregna
lactation, or in women of childbearing age requ
that its potential benefits be weighed against it
possible hazards.

Precautions: In the elderly and debilitat
and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to
preclude ataxia or oversedation, increasing gra
ally as needed and tolerated. Not recommende
in children under six. Though generally not re
ommended, if combination therapy with other
psychotropics seems indicated, carefully consid
individual pharmacologic effects, particularly i
use of potentiating drugs such as MAO inhibit
and phenothiazines. Observe usual precautions
presence of impaired renal or hepatic function.
Paradoxical reactions (*e.g.*, excitement, stimulat
and acute rage) have been reported in psychiatr
patients and hyperactive aggressive children.
Employ usual precautions in treatment of anxi
states with evidence of impending depression;
suicidal tendencies may be present and protecti
measures necessary. Variable effects on blood
coagulation have been reported very rarely in
patients receiving the drug and oral anticoagulants; causal relationship has not been establish
clinically.

Adverse Reactions: Drowsiness, ataxia a
confusion may occur, especially in the elderly a
debilitated. These are reversible in most instanc
by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In
few instances syncope has been reported. Also e
countered are isolated instances of skin eruption
edema, minor menstrual irregularities, nausea a
constipation, extrapyramidal symptoms, increas
and decreased libido—all infrequent and general
controlled with dosage reduction; changes in EE
patterns (low-voltage fast activity) may appear
during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic
dysfunction have been reported occasionally, ma
ing periodic blood counts and liver function test
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Perforations and Ruptures of the Esophagus. William S. Lyons, M.D., Michael G. Seremetis, M.D., Vicente C. deGuzman, M.D. and Joseph W. Peabody, Jr., M.D. 267

Temporal Arteritis: A Review of the Washington Hospital Center Experience with Comparison of the Literature. Gregory John Ladas, M.D. 273

Intractable Ascites During Maintenance Hemodialysis. Antonio Uy, M.D., Robert J. Shalhoub, M.D., J. M. Brian O'Connell, M.D., Mary J. Matthews, M.D. and George A. Higgins, M.D. 277

Application of Thermography in Peripheral Vascular Diseases. Baikunth K. Singh, M.D., F.R.C.P. (C), F.A.C.A. and Takeshi Motomiya, M.D. 280

A Statistical Study of Infants Born with Withdrawal Symptoms in the District of Columbia. William I. Barton, M.A. 287

Peutz-Jeghers Syndrome Case Report. Edward E. Cornwell, Jr., M.D., F.A.C.S., Masud Homayouni, M.D. and Frances Blackwell, M.D. 291

SPECIAL ARTICLES

F-Stop, Anyone? John M. Keshishian, M.D. 294

OTHER FEATURES

The View Box 317

ECG Problems 272

Book Reviews 303
  Current Diagnosis and Treatment 1973. (Krupp and Chatton) Reviewed by George A. Boinis, M.D.P.C.

  Pulmonary Reactions to Coal Dust. A Review of U.S. Experience. (Key, Kerr and Bundy) Reviewed by Bernard Grand, M.D.

(continued)

Vectorcardiography in Congenital Heart Disease. (Ellison and Restieaux) Reviewed by Stanley M. Silverberg, M.D.

The Language of Fractures. (Schultz) Reviewed by Stephen S. Haas, M.D.

Common Problems in Office Practice. (Taylor) Reviewed by Nelson G. Goodman, M.D.

Supportive Care of the Surgical Patient. (Stahl) Reviewed by John Stubenbord, M.D.

Hereditary Retinal and Choroidal Diseases (Krill) Reviewed by Stephen S. Pappas, M.D.

New Members 297

Obituaries 318

Classified Advertising 17

Index of Advertisers 18

Information for Authors 11

Advertising and Subscription Information 11

A COMBINED 1973 SCIENTIFIC ASSEMBLY

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Monte Carlo,
Monaco ....October 14–21

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PRESIDENT'S MESSAGE

Irving Burka, M.D.

What Price Health?

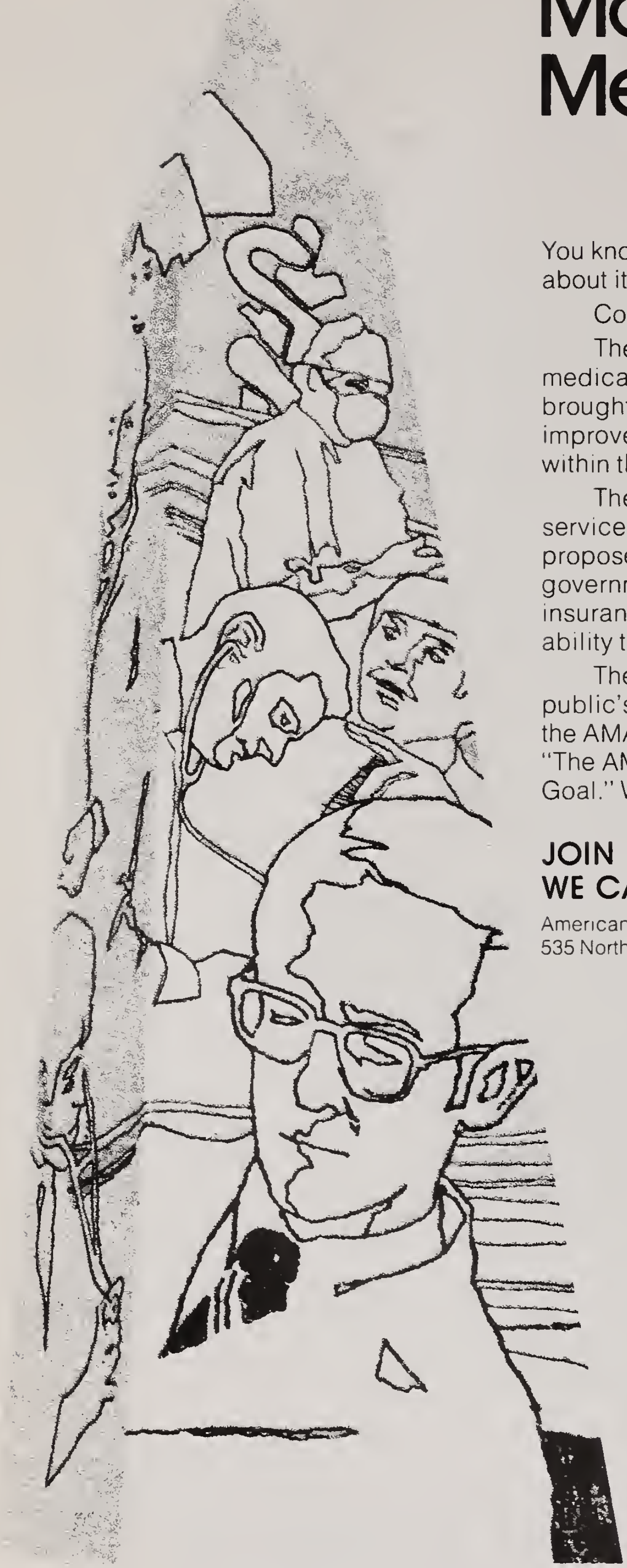
Several months ago NBC Television staged a much ballyhooed documentary on the state of health care in the United States, which was titled, "What Price Health?"

This program was presented on a nation-wide hook-up and seen by millions of people. It was purported to be a study in depth of the problems of health care delivery. A well known reporter and commentator narrated editorially on the various aspects of the state of health care in our country, usually in a destructively critical vein.

Pathetic case after pathetic case was paraded for the viewers in an effort to demonstrate how the high cost of health care is bankrupting many people, and preventing others from obtaining critically needed attention. One particular example stands out: that of a youngster who needed heart surgery but the parents could not afford the cost; hence the patient was totally incapacitated. The true facts, however, show that this child had been followed by very competent physicians in the community for several years. The cardiac defect was corrected as planned before the television program appeared or was even contemplated. Furthermore, NBC News conveniently failed to follow up on this case between interview of the family and the broadcast of the show. The excuse that the network gave was that the family had no telephone, and therefore, it was difficult to communicate with them.

It seems to me most incomprehensible that the largest news gathering network in the world found itself unable to contact one family so important to this program or to verify other facts of the program. The result produced a biased, distorted picture replete with falsehoods, half-truths, overdramatized witnesses and biased experts, all aiming to show that American medicine and the present health care delivery system are total failures. This is a mark of complete irresponsibility on the part of NBC. We requested equal time to answer the allegations but were denied that opportunity on two occasions. The denial was documented with pious proclamations and assurances as to the absolute righteousness of NBC.

As citizens and physicians, the health of our people is most important. We admit that there are deficiencies and inequitites in health care. How to remove these deficiencies and improve on our system of health care is a subject which should be explored objectively, without bias or prejudice. The media, particularly television, could play a vital role in this endeavor in accordance with the finest tradition of journalism. Freedom of the press should go hand in hand with responsibility and striving for truth.



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The AMA is working hard to protect your interests and the public's. But we need your support. Find out more about what the AMA is doing for you and the public. Send for the pamphlet, "The AMA and the American Doctor: Sharing a Common Goal." Write: Dept. DW, at the address below.

JOIN US.
WE CAN DO MUCH MORE TOGETHER.

American Medical Association
535 North Dearborn Street/Chicago, Illinois 60610

In Defense of Electroshock Therapy

Politics and EST are strange bedfellows. But following the "Eagleton affair" in July 1972, Electroshock Therapy (EST) became a household word when it was revealed that a candidate for the Vice-Presidency of the United States had been successfully treated for a psychiatric disorder with EST. Eventually his name was withdrawn from the ticket. Whether his withdrawal was prompted primarily by the nature of his past illness or by the nature of the treatment he received is still not clear. However, during the ensuing weeks and months, the American public was bombarded by a barrage of information and misinformation about psychiatry. Psychiatrists were sharply divided and the general medical profession itself was confused. Was EST harmful? Was it on the way out? Had it been supplanted by the newer chemical antidepressants and tranquilizers? What was the truth of the matter?

Electroshock Therapy or Electroconvulsive Therapy (ECT) has been with us since its discovery by Cerletti and Bini in 1938. When properly used, no somatic treatment in psychiatry has been as consistently or as dramatically effective over such a long period. During the past 35 years the procedure has been greatly refined and is now a well accepted treatment modality. But in some psychiatric centers it has fallen into disuse or worse, has been treated with disdain, often by psychiatrists who have had little personal experience with this procedure and seem to be guided more by emotion than by reason.

There seem to be many reasons for this state of affairs. There is no doubt that over the years individuals and groups have misused or abused EST for a variety of reasons. However, such practices are not confined to psychiatry. Any procedure in medicine which gains popularity and which is relatively easy to administer, is subject to the same abuse. Although this is no excuse, the so-called "shock mills" have contributed to the negative professional and public attitudes regarding EST.

Another factor contributing to the negative attitudes has been the dominance of psychoanalytic teaching in medical schools and in psychiatric residency training programs. Little time is given to teaching the indications and techniques of EST. The new generation of psychiatric residents includes many who have never administered, much less witnessed, an electroshock treatment. The attitude toward EST is often one of smug condescension. The psychiatrist who still administers EST is often regarded with the kind of disdain which gynecologists used to reserve for colleagues who performed "therapeutic" abortions in the old days before legalization. In many medical schools a double standard seems to exist. I have known psychiatrists who preach publicly against the use of EST but who have privately recommended it for members of their own family or for individual patients.

Still another reason for the negative attitude toward EST may be found in the scores of articles, horror stories in Sunday supplements, sensational books and plays (e.g. "One Flew Over the Cuckoo's Nest") which portray EST as a form of punitive therapy controlled by sadistic doctors and nurses. Anyone familiar with the workings of a modern psychiatric hospital with its insistence on clear criteria and informed consent can dismiss this as sensational hogwash which can only create needless anxieties in the minds of the suggestible lay public.

Electroshock Therapy remains, to this day, one of the most effective treatment methods for the rapid relief of severe depressive reactions and for various other severe psychiatric disorders. It should not be allowed to fall into disuse because of popular and professional prejudices based on erroneous information. If it is abandoned, patients will suffer. It is the responsibility of all psychiatric residency training programs to offer training in the indications for and the techniques of Electroshock Therapy. It is also the responsibility of those who administer EST to use it properly and to be more articulate in informing the medical and lay public about its effectiveness. Psychiatry, like medicine, is still an inexact science. But we should not condemn a treatment method such as EST which, when properly used, can eliminate certain types of otherwise intractable mental suffering.

ZIGMOND M. LEBENSOHN, M.D.

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Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Acute gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existence of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
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Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American Pharmaceutical Association

"Too many doctors are indiffe ent to the economic consequences their decisions." So stated a recent issue of *Medical News Report* (December 4, 1972), an independent weekly newsletter published by forn AMA Chief Executive F. J. L. Blasingame, M.D.

Doctor, are you indifferent . . . ?

In discussing an anticipated ir crease in Blue Shield rates, Dr. Blasingame's newsletter had this to say:

"In general, it can be said, MD have given the impression they are not particularly concerned with the increase in cost of health care to the patients . . .

"True, an MD's training is primarily scientific, but in the real worl of practice, all of his scientific decisions have a price tag, or an econom impact. The economics of health ca beckon the practitioner's attention. Concern for economics of medicine

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical Manufacturers Association

When the pharmacist recommends that a drug product other tha the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is necessary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, the unilateral decision of the pharmacist, made in the absence of clinical knowledge of the patient, could expose him to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothing in the pro-substitution argument that offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowledge about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degree, puts him at a disadvantage. Most often, a practicing physician will need expert knowledge of no more than 25

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ld be an obligation of medical
tice . . .

"Medical societies ought to con-
continuing campaigns to point
ne substantial savings that could
alized thru deductible insurance
protection for catastrophic ill-
. At the very least, they should, in
atients' interest, question the
cs of any insurance organization
raises health care costs by forc-
olicyholders to buy insurance
may not need or want and prob-
won't ever use.

"Too many doctors are indiffer-
o the economic consequences of
decisions. Too many, for ex-
le, habitually hospitalize patients
ne convenience of the MD. It's
sense to deny such habits exist . . .

"Doctors, thru their medical so-
es, have unhesitatingly appealed
eir patients for support in the
against government interference
the private practice of medicine.
the public in the past has re-
nded. It's time the American Med-
Association and state and local
ical societies paid off the debt by
sive action to hold down the cost
edical care."

of Drugs

Insurance rates and hospital
ges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned.* Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

---

0 drugs that he selects to treat the
ority of conditions encountered in
practice. Moreover, the physi-
's choice of a specific brand is
ed on his knowledge of the pa-
t's medical history and current
dition, and his experiences with
particular manufacturer's
duct.

Some substitution proponents
e argued that the dispensing of a
scription is a simple two-party
saction between the pharmacist
the patient, and that a substitut-
pharmacist may avoid even a
nical breach of contract by simply
fying the patient that he is making
substitution. I would judge that
courts would be sympathetic
ard a pharmacist who substituted
hout physician approval and who
ertook a legal defense that seeks
nake the patient responsible for
pharmacist's actions.

uced Prescription Prices?

Substitution advocates are
gesting to the consumer, and par-
larly the consumer activist, that
uced prescription prices could
ow legalization of substitution.
have seen absolutely no evidence
ustify this claim. To the contrary,
erience in Alberta, Canada, where
stitution is authorized, suggests the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands—of, say, ampicillin or tetracycline—or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

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SCIENTIFIC ARTICLES

Perforations and Ruptures of the Esophagus

WILLIAM S. LYONS, M.D.*, MICHAEL G. SEREMETIS, M.D.†,
VICENTE C. DE GUZMAN, M.D.‡ AND JOSEPH W. PEABODY, JR., M.D.§

Introduction

Perforations of the esophagus, spontaneous or iatrogenic, are very dangerous. It is said that without treatment they are 100% fatal, and practically speaking this is true. The condition is a dramatic one. The gut is open to the interior of the body and seemingly requires equally dramatic thoracotomy and direct suture for correction. While it may be true that no one survived before the era of surgical intervention, it is also true that across the board application of major surgery has left us with a substantial mortality still. The purpose of this paper is to suggest, through an examination of our own material in the light of the experience of others, areas where conservatism is likely to result in improved survival. This is not to suggest a change in treatment, which remains surgical, but to suggest a change in emphasis.

The perforated gut has always been looked upon as a surgical condition by surgeons and medical men alike. The need for direct closure has seemed elementary even to the layman. So throughly ingrained is the logic that in appendicitis, for example, no matter what the state or condition of the patient, the surgeon is under considerable onus to justify any delay or deferral of surgery. Laymen have felt driven under certain circumstances to try to remove an appendix, believing that death was certain if they did not. In this connection you may recall the celebrated submarine appendectomy carried out by the Captain and a pharmacist mate toward the close of World War II. In order to head off repetitions of this sort of surgery, papers began to appear in the U.S. Naval Medical Bulletin[1-3] indicating that in the absence of qualified surgeons, antibiotics may be used with safety in acute appendicitis until the patient could be transferred to a proper facility for further therapy. Many never had appendectomy.

In the early 1950's the surgical literature, especially in Great Britain, indicated that a new non-surgical era had arrived in the treatment of acute perforated peptic ulcers.[4-7] Large series treated with nasogastric tubes, parenteral fluids and antibiotics produced mortality rates of 6 to 8%. While time eventually showed that this method was not as good as surgery where death rates of 1 to 2% have been achieved, there is, when the circumstances warrant, a practical alternative to laparotomy.

Our experience would indicate that thoracotomy and repair of the esophagus is not the only nor necessarily the preferred treatment in cases of rupture of the thoracic portion. If the mortality is to be improved, alternative methods avoiding major surgery will have to be more frequently employed, especially in the very ill.

We have been impressed through the years with the fact that perforation or rupture of the esophagus will not lead necessarily to death without surgical closure, that reopening of the surgically repaired rent is alarmingly frequent,[8] and that the esophagus, properly assisted, has a remarkable ability to heal. Those facts are the basis upon which the conservative management of rupture or perforation of the esophagus is based.

We have said "properly assisted," the esophagus will heal itself—what this means is:

1. The organ is defunctionalized:
   a. There is no oral intake.
   b. Saliva is expectorated.
2. The edges of the rent are protected from acid, bile and

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enzyme attack by keeping the stomach drained.

3. Fistula development is encouraged by careful placement of pleural or mediastinal drains.

Discussion

In assembling the data for this paper, we were readily able to find 50 cases of this relatively uncommon problem in our own files and in the experience of the last two years of the Morris Cafritz Memorial Hospital and of the Washington Hospital Center. All of the cases but three were cared for by myself or my former associates: Drs. Edgar Davis, Joseph Peabody, Vicente DeGuzman and Michael Seremetis. We have a good knowledge of the remaining three, as they occurred on our services at the above hospitals. We would like to emphasize that in most cases we were asked to attend the patient after perforation had occurred.

Figure 1 shows the causes of esophageal perforation and all are represented in our series with the exception of the passage of tubes such as the Blakemore Saengstaken tube. This tube has been known to cause rupture of the esophagus by forcible extraction by the patient with the balloons inflated or by inflation of the balloons in an incorrect position. Non-iatrogenic perforations would include perforation by foreign bodies which in this present series included bullets, a pencil, glass fragments, pins, and fish or chicken bones. The classic non-iatrogenic perforation is the so-called spontaneous full thickness rupture or Boerhaave's Syndrome.

Herman Boerhaave was the first to describe spontaneous rupture of the esophagus. His clinical description in 1726 was so complete and accurate that there is little to add today. He was called upon to attend the Admiral of the Dutch Navy who had gorged himself on duck and, having deliberately induced vomiting, was suddenly seized by a severe pain in the left chest. The Admiral went on to die in the next 24 hours, and post mortem examination revealed the rent in the lower esophagus and the remains of duck and other parts of the meal swimming in the left pleural space. It is of some interest and certainly no accident that it was this same Boerhaave who first localized pleurisy to the pleura.

Esophageal Perforations

I. Iatrogenic (most frequent)
    A. Endoscopy
    B. Esophageal Dilatations
    C. Passage of Tubes
    D. Major Thoracic Surgery

II. Non-Iatrogenic Perforations
    A. Missiles
    B. Foreign Bodies
    C. Spontaneuous Rupture (Boerhaave Syndrome)

FIG. 1.

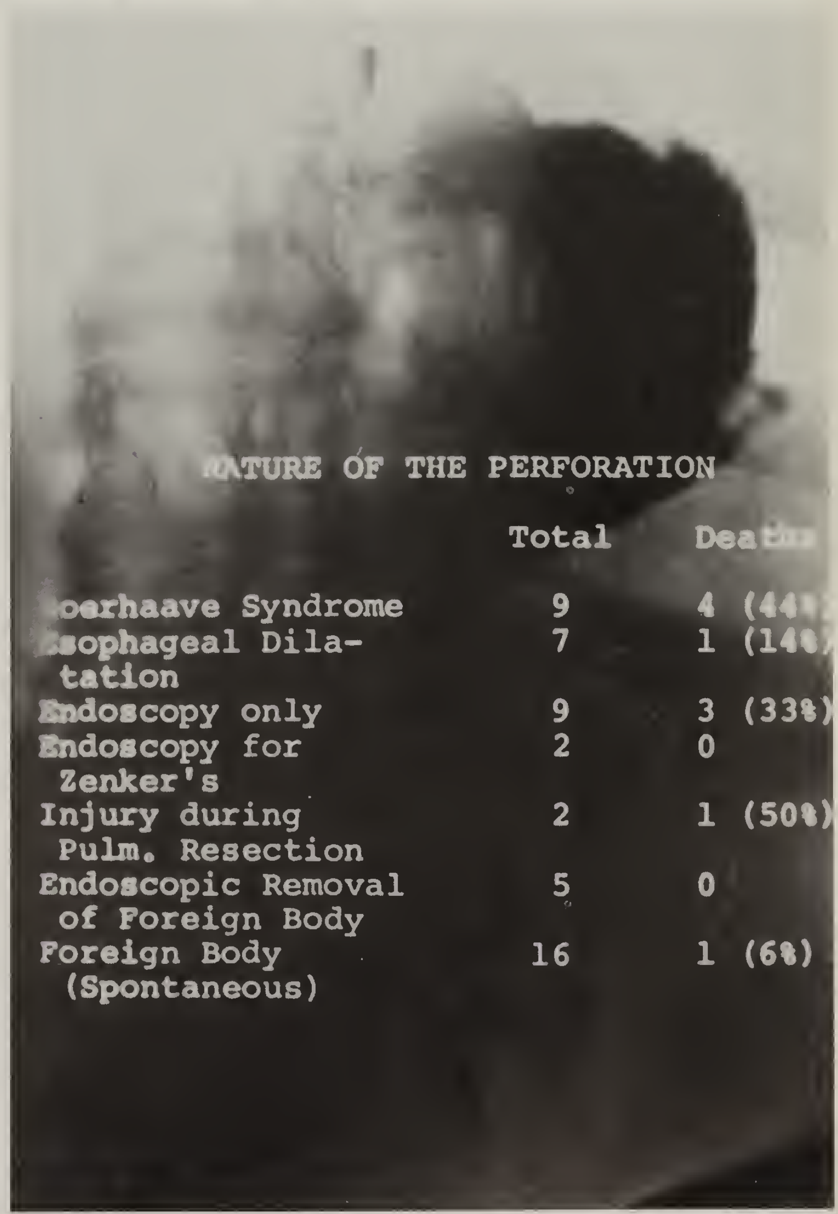
Figure 2 shows the nature and distribution of the 50 perforations with the mortality experienced in each group. The highly lethal nature of spontaneous rupture of the esophagus is evident. Of the four deaths, one died essentially without diagnosis and another was mistakenly operated upon for another condition. The one death following dilation was associated with pneumostatic dilation of a patient with achalasia. Three deaths in nine instances of perforation following diagnostic endoscopy certainly raise the eyebrows; two were due to delayed drainage of the neck in cervical perforations, one followed esophagoscopy and perforation of the lower third. The fact that two perforations were associated with esophagoscopy in the presence of a Zenker's diverticulum confirms the generally known fact that a Zenker's raises the risk of endoscopy considerably. In both these cases, the perforation was suspected, confirmed within a few hours of endoscopy, and the diverticulum excised at the time of cervical mediastinotomy. Injury to the esophagus during pulmonary resection almost invariably is associated with benign disease. The one fatality here was recognized very late, and repair was followed by dehiscence. It is difficult to separate spontaneous perforation of the gullet by foreign bodies from perforation during their removal. Nevertheless, of 21 cases of this nature only one patient was lost, due to failure to recommend endoscopy at the time of suspected lodgment of the foreign body.

Figure 3 shows the distribution of our cases according to level and the mortality related to the level of perforation. Our experience is representative of that in the United States generally. A recent report by Youngs and Nicoloff, of 50% mortality of perforation in the cervical region, while emphasizing the real danger of the perforation is surely not typical. Perforation of the thoracic esophagus is far and away the more dangerous. The 100% mortality of the middle third suggests that the two cases at that level were probably unusual. One was an operative injury during pulmonary resection; the other a perforation of a chicken bone into the pericardium. The 31% mortality for perforations and ruptures in the lower third, while probably typical nationwide, represents the area where a change in conventional management could be rewarding. Of the 19 patients in this group, nine were of the classical Boerhaave Syndrome and four of these were lost. Ten were instrumental ruptures or perforations. Of the ten, five showed the typical systemic reaction together with evidence of mediastinitis and pleuritis similar to Boerhaave Syndrome. Two died after thoracotomy and repair; two lived. A fifth barely survived with closed thoracostomy and gastrostomy. The remaining five were recognized early and handled without complication.

Boerhaave's Syndrome was said to have been 100% fatal prior to 1946 when N. R. Barrett reported the first surgical attack on the problem. In this first patient the esophageal repair dehisced, a fistula formed and convalesence was prolonged. In all probability survival was possible because of the drainage provided by the fistula. Under the most vigorous surgical approach today, mortality remains in the 30-40% category in Boerhaave's Syndrome. Instrumental perforation can be equally dangerous, as our experience shows, if diagnosis is delayed and mediastinitis and pleuritis have a chance to develop.

All authorities recognize the adverse effect on survival rate of delay in the institution of therapy. Wychulis and associates at the Mayo Clinic emphasize that spontaneous perforations are lethal if treatment is delayed over 24 hours.[9] In an excellent comprehensive paper on spontaneous perforations Abbott noted the high rate of repair dehiscence and death in those operated after 12-18 hours.[8] Generally speaking, at 24 hours after perforation the surgeon is looking at a patient with perhaps a 50% chance of survival. This fact should condition the course of therapy selected.

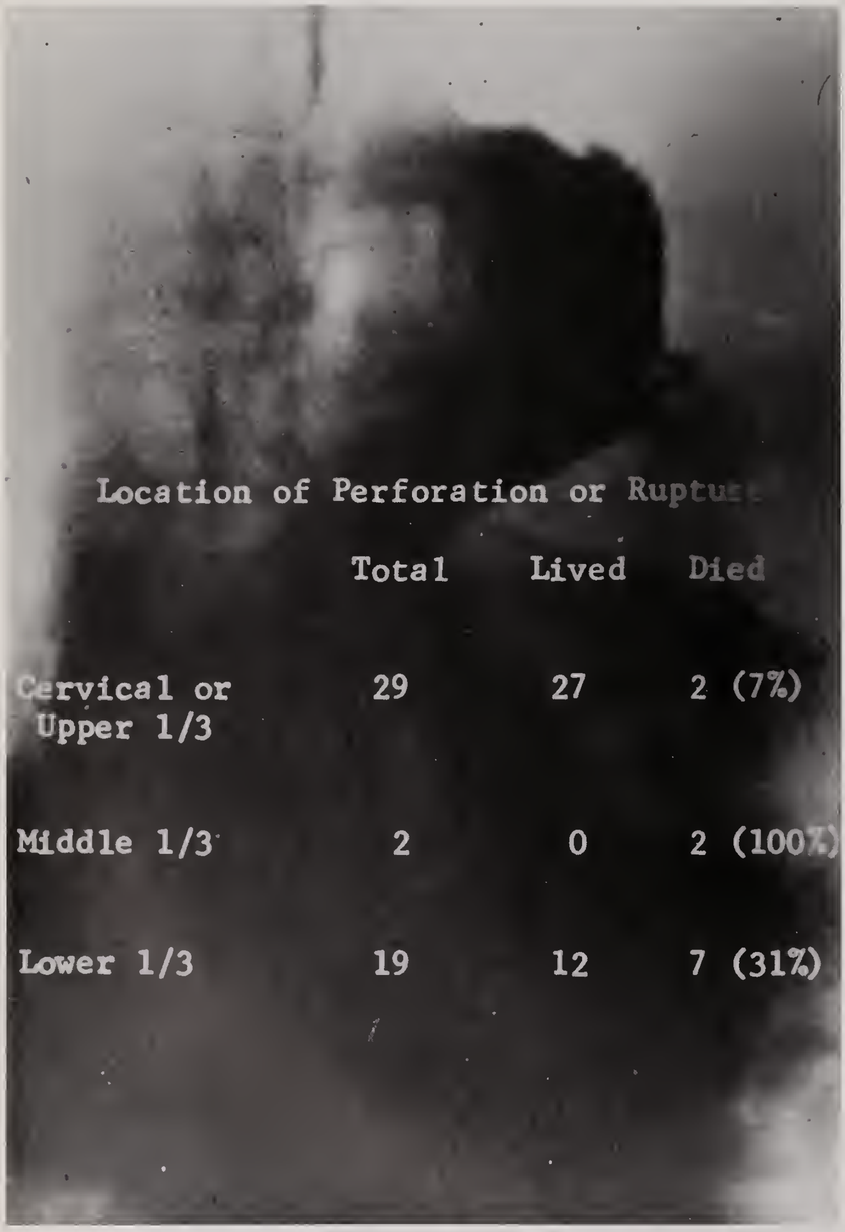
While surgical treatment and indications are fairly well standardized in the case of cervical perforations, they are not, in our view, in cases of intrathoracic perforations including Boerhaave's Syndrome. Two papers on esophageal perforations have appeared in important thoracic surgical journals in the past year. Loop and Groves well summarize current thinking by emphasizing the old surgical axiom that "the patient is too ill not to operate."[10] For authority N. R. Barrett is quoted: "Conservative therapy is likely to fail in that if the emergency is survived, the patient is apt to develop essentially untreatable mediastinal and pleural complications." In other words, a primitive logic prevails, the contents of the gut are leaking into the interior



NATURE OF THE PERFORATION

	Total	Deaths
Boerhaave Syndrome	9	4 (44%)
Esophageal Dilatation	7	1 (14%)
Endoscopy only	9	3 (33%)
Endoscopy for Zenker's	2	0
Injury during Pulm. Resection	2	1 (50%)
Endoscopic Removal of Foreign Body	5	0
Foreign Body (Spontaneous)	16	1 (6%)

FIG. 2.—Mortality related to the nature of the esophageal rupture or perforation; includes all cases whether treated by major or minor surgical procedures, or not treated.



Location of Perforation or Ruptu

	Total	Lived	Died
Cervical or Upper 1/3	29	27	2 (7%)
Middle 1/3	2	0	2 (100%
Lower 1/3	19	12	7 (31%)

FIG. 3.–Mortality of esophageal rupture or perforation related to location. Includes all cases however treated endoscopically or surgically. The greatly increased danger in thoracic perforation is evident.

of the body; death will result unless the rent is closed. Therefore thoracotomy and repair is the only solution–never mind that the esophagus is frequently in no condition for suture or that the patient is too toxic for surgery of this magnitude. Abbott too, in the article referred to above, seems compelled to attack the esophagus directly although the high rate of repair breakdown obviously has given him pause. Direct closure is not always necessary in our opinion. Dehiscence is so frequent that all who care for these patients must be impressed that integrity of the repair is not the essential element in survival. Foster, six years ago, was a strong advocate of direct suture of the laceration.[11] In 1970 his stance had changed considerably, advocating suture of the laceration "when appropriate" pointing out that drainage was the really important thing.[12]

As architects of the vigorous surgical approach, Loop and Graves have recommended that ancillary procedures be carried out as indicated at the time of thoracotomy and repair of the rent.[10] For example, Heller procedures, hiatal hernia repair, even esophagogastrectomy or esophagogastrostomy, in addition to repairing the rent, have been advocated. Six years ago Foster was also of this opinion. In a condition with the mortality rising approximating two per cent per hour, such recommendations strongly deserve to be questioned. There were two patients in the present series in whom ancillary procedures were carried out in addition to repairing the rent in the esophagus; both died. A hiatus hernia was repaired in one and a Heller procedure and hernia repair performed in the other.

Extensive experience with cervical perforations shows that suture of the laceration is unnecessary. With adequate drainage the esophagus will usually close promptly. Occasionally a temporary fistula will form. With respect to the thoracic esophagus, Foster states (in 1970) that with the combination of drainage and antibiotics closure will be prompt.[12] Such has been our experience with conservative management of thoracic perforations and ruptures, and with the spontaneous closure of dehisced repairs. As mentioned above, the high rate of dehiscence of primary esophageal repairs (nine of 13 in Abbott's series; five of 11 in ours) suggest that repair or lack of it is not the essential element in survival. The establishment of a fistula is essential, however. For this, open thoracotomy is not required.

In the combined group of lower third perforations, both spontaneous and instrumental, repaired by direct suture, there were four deaths for a mortality of 36%. While generally both mortality and dehiscence of the repair are thought related to delays in treatment, exceptions are frequent and no particular relationship is apparent in this series of eleven.

Improvement in management is necessary if the death rate in spontaneous and iatrogenic perforations of the lower third of the esophagus is to be reduced. The key to a successful outcome is prompt recognition. It is particularly important to us all that iatrogenic perforations survive; there is really no excuse for late diagnosis. Second, all oral intake must be stopped from the moment the diagnosis is suspected. Third, the stomach must be kept empty of acid juices and bile; a well functioning nasogastric tube or gastrostomy is necessary for this if the pleural space is involved, it must be adequately drained and the lung. If collapsed, promptly re-expanded. Closed thoracotomy, perhaps multiple as suggested by Abbott,[8] is indicated. Antibiotics are crucial in all cases and steroids vital in those cases with toxicity and evidence of extensive internal soilage.

The role of thoracotomy and closure of the perforation is not easy to assess. Surely the axiom that "the patient is too sick not to operate" is not correct. The burden of thoracotomy in the desperately ill can only contribute to an unfavorable outcome. In those patients diagnosed early and showing only slight to moderate toxicity, thoracotomy and suture of the esophageal rent may be the procedure of choice. If the repair holds, morbidity will be considerably shortened. If the repair reopens, which is common, thoracotomy should have afforded the best possible placement of drainage tubes in the pleura and mediastinum. On the other hand, consider the following two cases treated conservatively. In the first, rupture occurred during dilatation of an esophageal stricture. It was suspected and promptly confirmed at the first rise in temperature. Cessation of all oral intake, utilization of a previously existing gastrostomy, parenteral fluid support and antibiotics produced healing in four to five days. The second, is one of Boerhaave's Syndrome. Free rupture into the pleural space had occurred. The patient was hypotensive and very toxic. Treatment consisted of closed thoracostomy, nasogastric tube, antibiotics and steriods. Recovery was uneventful. About three weeks later he underwent laparotomy and gastroenterostomy for an obstructing carcinoma of the stomach.

Summary

Perforations of the esophagus are very dangerous, especially in the thoracic portion. In cervical perforations mediastinotomy is indicated if cessation of oral intake, parenteral fluid replacement, and administration of antibiotics is followed by the development of any local signs of inflammation. Perforations of the thoracic esophagus are probably best treated by major thoracotomy, if the repair can be carried out within 12 to 18 hours of the perforation and if toxicity is absent or minimal. However, if toxicity is significant, even within a few hours of the perforation, it is our opinion that survival will be improved if major surgery is deferred and the conditions set for spontaneous healing through drainage of the stomach and pleural space. We feel that ancillary procedures such as the Heller Operation and hernia repair are inadvisable in the acute situation unless, perhaps, the diagnosis is made very early and there is absolutely no toxicity present. The objective is survival in this dangerous condition; hernias and other problems can wait.

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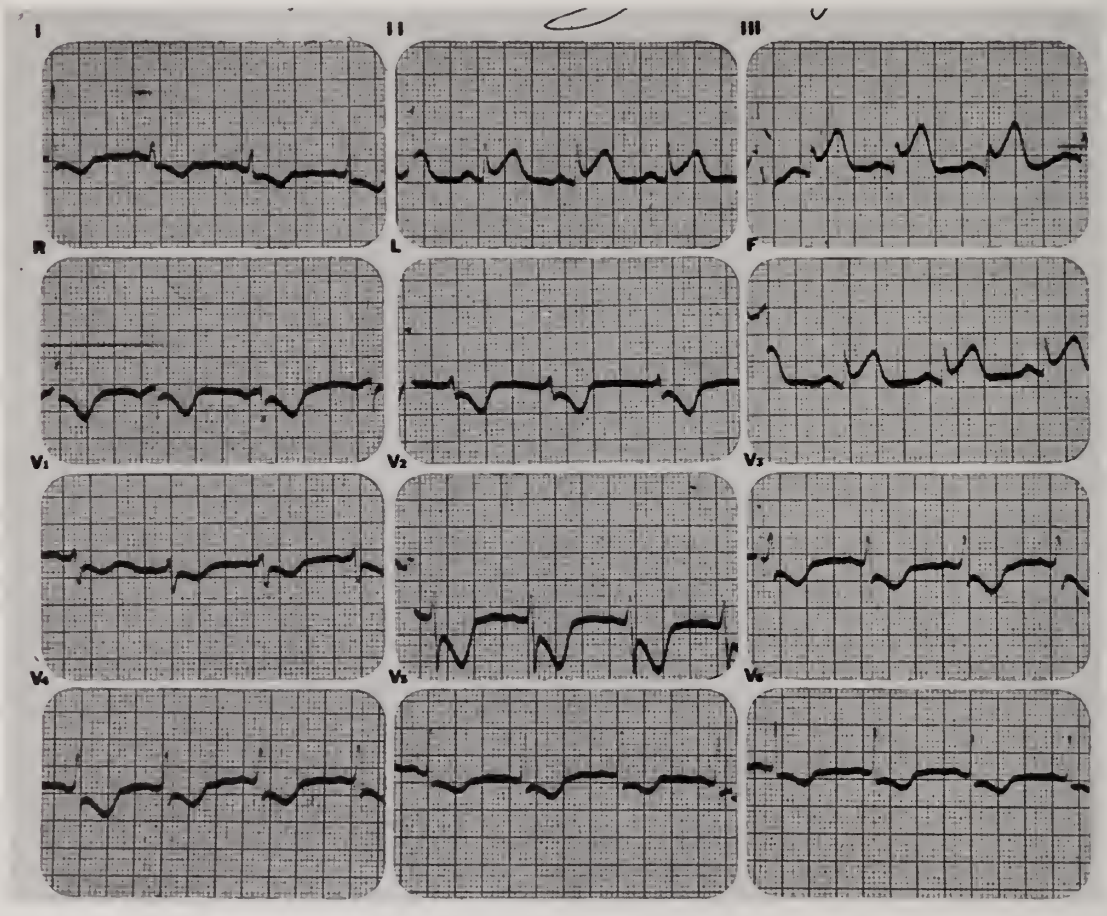
ECG Problems

HISTORY: 40-year-old housewife with intermittent pain in the anterior chest and arms for four days. Washed clothes, pain recurred, associated with sweat, and patient came to Emergency Room for advice. Previous health good. Grava II, Para II. Last menstrual period 20 days before onset of present illness. Not taking contraceptive pills.



INTERPRETATION: 1. ST-T changes consistent with acute myocardial injury.

The ST segments are abnormally elevated in leads II, III, and aVF, and even though their contour remains concave upward, the elevation alone suggests injury. The ST segment depressions in leads I, aVL, and all the precordial leads are consistent with ischemia or with inferior wall injury. Since there are no significant Q waves, a diagnosis of myocardial infarction cannot be established.

This patient was promptly admitted to a Coronary Care Unit where serial electrocardiograms demonstrated typical evolution of the changes of inferior wall (diaphragmatic wall) myocardial infarction.

Young, previously healthy, menstruating women who are not taking contraceptive pills and who do not have significant lipid disturbances still do have myocardial infarctions. This patient is one of those.

Edited by Robert R. Montgomery, M.D.

Temporal Arteritis: A Review of the Washington Hospital Center Experience With Comparison of the Literature*

GREGORY JOHN LADAS, M.D.†

Historically, the diagnosis of temporal arteritis dates back to 1890 when Hutchinson described a patient with painful temporal arteries. The entity was re-introduced to the literature in 1932 by Horton who discussed several older patients with severe headaches and associated painful temporal arteries. It was not until 1938, however, that Jennings noted the association of acute blindness in patients with inflamed temporal arteries. In 1960, Paulley discussed the relationship of temporal arteritis with polymyalgia rheumatica, and in 1962, Cogan introduced the concept of occult temporal arteritis.[1]

The literature is replete with references to the etiology of temporal arteritis.[2,3] A spectrum ranging from auto-immune reaction to the media of an artery, to micro-emboli involving the vasa-vasorum has been suggested. J. Lawton Smith has documented a case in which aluetic origin was suspected from the finding of the T. pallidum, within the wall of the involved artery. Others have suggested the Bedsonia-LGV virus, Actinomycetes, and possible drug allergy. With this formidable list, it is obvious that the etiology remains obscure.

Indeed, temporal arteritis has been a great mimic of many diseases. Often, because of its sly and subtle nature, the diagnosis remains a puzzle until much time has passed. It is this delay which all too frequently leads to visual loss. Because the visual problem occurs at a time of life when individuals depend on sight for most of their sensory input and activity, and because the condition represents a treatable one, an understanding of the entity is essential. Moreover, because of the varied presentation of this condition, many specialty services may be involved in the initial evaluation.

A retrospective analysis was undertaken of the clinical spectrum of temporal arteritis seen at the Washington Hospital Center during the years 1966-1971. Bias is part of a retrospective study reflecting, in large measure, the author's prejudices as well as the complexities in interpreting the terminology and coding of other physician's records. For this reason, comparison of our experience with that of the available literature is constantly stressed.

A review of medical records from all services at this hospital disclosed thirty patients in whom the diagnosis was considered. Fifteen of these fulfilled the diagnostic criteria, and of these, seven were biopsy positive, while the remainder had classic signs and symptoms of temporal arteritis and no evidence of other etiology. The biopsy need not be positive for the diagnosis to be made or for treatment with steroids to be initiated. The diagnostic criteria classically include age over 55; fever, malaise, anorexia, weight loss; angina of jaw or tongue; severe temporal headache or scalp pain; enlarged, nodular, tortuous temporal arteries; elevated sedimentation rate; sudden onset of visual loss in association with the preceding findings. In our series, the patients most often mentioned a preexisting "flu-like" illness. Noteworthy, however, no respiratory symptoms occurred, and a few had malaise significant enough to seek medical advice.

Severe unilateral or bi-temporal headaches occur and a peculiar pain in the jaw on chewing, secondary to claudication, is common according to most of the literature.[5] This latter finding was described in only one of the 15 patients in our series, however. A markedly elevated sedimentation rate is also common during this stage.[6] Other lab studies that have been promoted as valuable in the diagnosis include serum protein electrophoresis which may demonstrate a decreased albumen peak in association with an increased alpha$_2$ globulin level. Only one patient in our series had this test performed, and indeed, this pattern

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occurred. It should be made clear, however, that the pattern reported is a non-specific one occurring in many inflammatory conditions, and therefore, is probably not much better than the erythrocyte sedimentation rate as such. It is useful, nevertheless, in conjunction with tests for rheumatoid arthritis factor and LE preparations in ruling out other causes of angiitis.[1]

The visual disturbance, itself, is delayed a variable amount of time following the onset of the constitutional reaction, but usually occurs within two to three weeks.[1] To complicate matters, a form known as occult temporal arteritis has been described where the loss of vision heralds the disease and no history of pre-existing systemic illness can be elicited.[6,7,8,9] Some investigators feel this is the most common form.[10]

The classic appearance of the involved temporal artery includes marked tortuosity, nodularity, and surrounding erythema. Pain and tenderness over the artery are common. In our series, the prominence of the arteries and the amount of pain and tenderness was of an extremely variable nature.

Pathologically, the process begins in the media of the vessel, and not in the elastica as once thought.[2] Swelling and degeneration of smooth muscle cells (Stage A) is the earliest sign according to Reinecke and Kuwabara.[2] Breakdown and proliferation of the intima occur as a secondary reaction. Two features are important here. First, giant cells are plentiful only during the second stage (Stage B), a biopsy report negative for giant cells does not necessarily mean negative for temporal arteritis. In our series, one biopsy fell into Stage A and was initially diagnosed as a non-specific arteritis, when in reality it could be considered a positive biopsy for temporal arteritis. The second important point concerns the well known segmental or patchy involvement of the artery, and because of this, unless an involved portion is obtained, the biopsy report will be returned as negative. A repeat biopsy is therefore of much value when the index of suspicion persists. One patient in our series had a repeat biopsy, and, indeed, this was positive. The third stage (Stage C) is the chronic reparative phase with rare giant cells and a fibrotic media.

Further analysis of our patients showed that approximately one-half (seven of 15) had the picture of classic temporal arteritis. Four of the fifteen patients presented with loss of vision without other symptoms, in other words, in the occult form. This contrasts with the literature already cited which suggested the occult form to be the most common. Interestingly, the remaining four patients gave histories compatible with polymyalgia rheumatica, a syndrome characterized by pain and stiffness of the muscles of the neck and shoulder girdle and thought to be a part of the spectrum of diseases reflected by giant cell arteritis. Constitutional symptoms as well as an elevated sed rate are also present in this condition.[4,11,12] We will see later in our study the range of specialty services that become involved in the diagnosis prior to the onset of visual disturbance, because of the varied symptoms.

The mean age in our group of patients was 71 with a range of 58 to 84 years. These figures are in close agreement with the literature.[1] Surprisingly, however, women predominated in our study, comprising 14 of the 15 patients. The information available usually cites equal incidence in the sexes. More recently, however, a study at the Mayo Clinic revealed a 4:1 female to male ratio.[13] The reasons for the increased incidence in the female population are obscure but may be a reflection of the fact that more women live long enough to acquire the disease.

Also important to note is that in no case was the sedimentation rate greatly elevated in our group of patients. The normal value in our laboratory is less than 20 (Wintrobe, corrected) in females, and the mean value in our patients, pre-treatment, was 40 with a range of 31-48. Most of the literature already cited stresses that the sedimentation rate is highly elevated with the range extending to 100 by the Wintrobe method. The reasons for this disparity are not clear but may reside in laboratory variation of the technique or in the clinician obtaining this test before or after the peak of inflammatory activity.

It is important for the clinician to realize that although only four of the 15 patients had the occult form of the disease, in reality, an additional five patients waited for visual loss to occur before they felt the need to seek medical attention.

Headache was the next most common symptom leading a patient to seek care, and in one case, tempero-mandibular joint pain prompted a patient to see an otolaryngologist who treated the involved joint with local steroids, unfortunately not enough to prevent the visual loss which followed and finally pointed to the true etiology.

The significant bilaterality of the visual disturbance is accentuated by its incidence in six of the 15 patients; i.e. more than one-third in our series suffered binocular visual loss. Other investigators cite a similar incidence.[14] The incidence of visual loss per se is quite high and occurred in two-thirds of the patients. Walsh claims that approximately one-half of the patients with this disease develop visual loss.[1] Presumably, the disparity here rests in the small number of patients in our series. That the visual disturbance is severe is shown by the fact that of sixteen eyes with previously known normal visual acuities, ten were left legally blind.

The single entity most responsible for visual loss was ischemic optic neuritis. Fully three-fourths of the involved eyes demonstrated this. In 13 of the 15 eyes involved, ischemic optic neuritis was the only finding, while in the other two, associated branch and central retinal artery occlusion were found. The other five eyes demonstrated ischemic retinopathy which was not further specified. In 1957, Wagener and Hollenhurst emphasized that ischemic optic neuritis was the most common ocular lesion encountered.[15] Other ocular findings which have been described in the literature include bruits over the eyeball[16] and diplopia.[17] None of these were described in our series. One of our patients did have the previously unreported findings of sludging and "beading" of the conjunctival vessels of the involved eye, suggesting the generalized decrease in blood flow to the eye. This finding was unilateral and present before ischemic optic neuritis was evident. Ischemic optic neuritis, the most common finding and therefore the most important, is recognized as a pale, mildly swollen disc with minimal to moderate narrowing of the retinal vessels. Initially, the changes are subtle and difficult to diagnose even by the oculist. Too often, the diagnosis is not defined until involvement of the second eye occurs. In our series, a time lag of two days to two months occurred prior to involvement of the second eye. Classically, one to ten days is cited.[1]

There were 15 patients that underwent temporal artery biopsy and did not fulfill the major criteria for diagnosis as previously outlined and in whom the biopsy was considered negative for temporal arteritis. Most of these patients had been considered for biopsy because of non-specific headache and/or visual disturbance. In the majority of these patients (11 of 15) no definite diagnosis was made. The other four patients were discharged with the diagnoses of periarteritis nodosa, diabetic retinopathy, central retinal artery occlusion, and vasculitis, type unspecified.

Regarding forms of the disease associated with a higher percentage of positive biopsies, three of seven patients with the classic form, two of four with the occult form, and two of four associated with polymyalgia rheumatica had positive biopsies. Thus, the incidence of a positive biopsy is not more likely to occur in one form of the disease over another, at least in our small series.

As expected, ophthalmology accounted for the majority of admissions, but neurosurgery and internal medicine were also represented. Indeed, two patients underwent extensive neurosurgical evaluation; one patient received an orthopedic evaluation because of the neck and shoulder girdle involvement and was subsequently treated with cervical traction prior to diagnosis; another patient, previously mentioned, was treated for tempero-mandibular joint pain by an ENT specialist. These incidents underscore the ability of this disease to masquerade as either a more ominous condition leading to many unwarranted diagnostic procedures, or on the other hand, as a relatively benign condition requiring only local therapy. The literature is replete with the searches for brain tumor, trigeminal neuralgia, dental problems, and hidden cancers.[11,18]

The visual fields have been cited as important in the diagnosis of ocular involvement. Most authorities claim an altitudinal field defect as the most common.[15] Only four patients in our series had visual field studies performed. This does not reflect ignorance of the significance of this study since, as already pointed out, many of the involved eyes were so functionally damaged that fields were impossible to perform. Nonetheless, the four patients who had fields, (total of five eyes involved) had field defects divided equally between 1) altitudinal, 2) superior temporal field cut, 3) arcuate scotoma, 4) paracentral scotoma in one eye with a fixation field in the other eye.

High dose steroid treatment has been credited with prevention and control of both systemic and ocular aspects of the disease.[19,20] In our series, one patient suffered visual loss of the second eye despite high dose steroids initiated twenty-four hours before. Two other patients had progression of visual loss while on steroids. It appears that steroids must be given early to prevent visual loss. This fact has been cited in the literature.[19] Visual improvement after initiation of steroids has also been recorded.[20] In our series two patients allegedly had visual improvement after steroids were started, but these were not well documented.

Also to be considered in the treatment of temporal arteritis are the problems related to high dose, long term steroids. Dosages as high as 100 mg. Prednisone per day for many months are not uncommon. In our series, two patients were reported to have become Cushingoid, and one patient developed a fatal septicemia. This latter patient was on steroids for over a year because the condition could not be controlled after several attempts to wean the patient from medication.

Our study included no long term follow-up of the bulk of the patients. However, the long term prognosis of patients with this condition has been questioned with some evidence that the mortality rate is 10 to 20% with death resulting from cerebrovascular accident, myocardial infarction, or ruptured aortic aneurysm.[21] Alternatively, a more recent study at the Mayo Clinic showed no evidence of a reduced survivorship in individuals who had temporal arteritis.[13]

In summary, the spectrum of temporal arteritis at the Washington Hospital Center has been presented and contrasted to that in the literature. The visual severity of this entity was emphasized noting that early diagnosis is important if one is to prevent visual loss. It was further emphasized that the diagnosis rests on a high clinical suspicion with laboratory and biopsy results only of secondary importance. Lastly, the varied aspects of the disease were delineated in hopes of alerting the various medical and surgical sub-specialties of the patch-work of signs and symptoms which might lead a patient to seek attention from their particular specialty prior to onset of visual loss.

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Intractable Ascites During Maintenance Hemodialysis*

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Uremic pericarditis is a well recognized complication of renal failure and one which may also occur despite maintenance dialysis.[1] Less well recognized is unexplained pleuritis which may also be observed in this group of patients.[2] Recently ascites has also been reported, in abstract form, but other than for an association with an ominous prognosis, no details are presented.[3,4] The purpose of this communication is to report a patient on maintenance hemodialysis who developed intractable exudative ascites during the early months of therapy which resulted in severe disability and seriously impaired efforts at rehabilitation. An extensive diagnostic search including exploratory laparotomy revealed non-specific inflammatory changes on peritoneal biopsy.

Report of Case

J.G. is a 34-year-old black man with end-stage kidney disease secondary to chronic glomerulonephritis who was transferred from another hospital for hemodialysis. At the age of 21, he was hospitalized for acute glomerulonephritis but was released without follow-up. At the age of 28, he contracted pulmonary tuberculosis and was treated for one and one-half years with ethambutal, para-aminosalicylic acid and isonicotinic acid hydrazide. At age 30 he was found to be hypertensive and azotemic and was started on drug and dietary therapy. Two years later he was hospitalized at another hospital for uremia. Peritoneal dialysis was started and repeated at weekly intervals until hemodialysis was begun after three months. His early course was complicated by an episode of pericarditis resulting in hemopericardium and cardiac tamponade which responded to pericardiocentesis and peritoneal dialysis. He was subsequently transferred to the Veterans Administration Hospital, Washington, D.C., and treatment was started with chronic hemodialysis in March, 1969. Dialysis has been performed 20 to 30 hours weekly on a standard Kiil dialyzer. About four weeks after the institution of hemodialysis, the patient began to accumulate massive ascites without peripheral edema of signs of pericarditis or congestive heart failure. Average predialysis blood urea nitrogen and serum creatinine were 75 mg% and 15 mg% respectively. Multiple diagnostic paracenteses revealed negative smears and cultures for acid fast bacilli, bacteria and fungi. Cell count revealed 310 WBC/mm^3 with 6% neutrophiles, 5% lymphocytes, and 89% mesothelial cells. Several subsequent cytological studies again revealed a preponderance of mesothelial cells, some of which were described as atypical. Lactic dehydrogenase activity was normal and ascitic fluid protein ranged from 2.8 gm% to 3.8 gm% with a serum albumin of 2.9 gm% to 3.3 gm%. Serum amylase, protein bound iodine and several lupus preparations were normal. A lymphangiogram revealed a normal lymphatic system along the femoral, pelvic, and the abdominal chains of lymphatics. Liver scan and liver function tests were normal. More frequent dialysis and ultrafiltration was commenced but was limited by hypotension without adequate mobilization of the ascitic fluid. The abdomen was tapped for relief of symptoms on several occasions, but the fluid reaccumulated after several days. Because of the patient's previous history of uremic pericarditis and pulmonary tuberculosis, a cardiac catheterization was done which showed no evidence of constrictive pericarditis. The patient's ascites was incapacitating because of symptoms of abdominal discomfort, nausea, vomiting, and inadequate dietary intake. Because of the negative work-up and continued diagnostic uncertainty, an exploratory laparatomy was carried out. 8500 ml of yellow ascitic fluid was aspirated from the peritoneal cavity. On gross examination the kidneys were contracted, the peritoneum appeared to be thickened and the retroperitoneal and mesenteric nodes were slightly enlarged. The exploration was otherwise normal. Biopsy specimens were taken of the liver, lymph nodes and parietal peritoneum. Microscopic examination of a lymph node revealed preservation of the nodal architecture with marked hyperplasia of reticuloendothelial cells lining sinusoids. The node contained lipid laden macrophages and fat vacuoles. There was no evidence of malignancy. Pathologic diagnosis was reactive hyperplasia with lipogranulomatosis. Sections of the liver revealed a normal thin intact capsule with normal hepatic architeçture (Fig. 1). The Kuppfer cells were moderately swollen but the liver was otherwise normal. The peritoneal biopsy specimen measured 2 x 0.8 cm. One surface was smooth, glistening and opaque; the other, hemorrhagic and roughened. On microscopic examination, the parietal peritoneum was thickened, fibrotic and covered by a vascular fibroblastic proliferation which was infiltrated by rare mononuclear cells. There was no evidence of granuloma or malignancy. The pathological diagnosis was mild, non-specific, chronic fibrosing peritonitis (Fig. 2). Recovery was uneventful except for recurrence of the fluid. The ascites was finally reduced to a tolerable amount 10 months after surgery during dialysis treatment with ultrafiltration and a tight abdominal binder. During this period he also developed an unexplained pleuritis with a sterile exudative effusion and non-specific fibrinous pleural changes on needle biopsy. This finding was felt to be consistent with what others have called uremic pleuritis.[2] He is currently doing well on home dialysis and has no clinical evidence of ascites.

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Discussion

Because intractable ascites is uncommon in well dialyzed patients on chronic hemodialysis programs, an exhaustive search for the usual causes of ascites was carried out. Ruled out in this work up were tuberculosis, neoplasm, bacterial and fungal infection, liver disease, myxedema, constrictive pericarditis, lymphoma, lupus erythematosis and granulomatous disease. Indeed the major abnormality noted consisted of non-specific chronic inflammatory changes on the parietal peritoneum. The etiology of these findings is uncertain. One possibility is that the previous peritoneal dialyses over a three month period could have produced these inflammatory changes by repetitive catheter-induced mechanical irritation of the peritoneal surface or by chemical irritation due to the inadvertent introduction of talcum powder or particulate material into the peritoneal cavity. While the majority of our own patients receive one peritoneal dialysis prior to commencing chronic hemodialysis, this patient received 12 at another institution. Another possibility is that in addition to pericarditis and pleuritis, serosal involvement in protracted renal failure may also include the peritoneum. The fact that this patient also developed

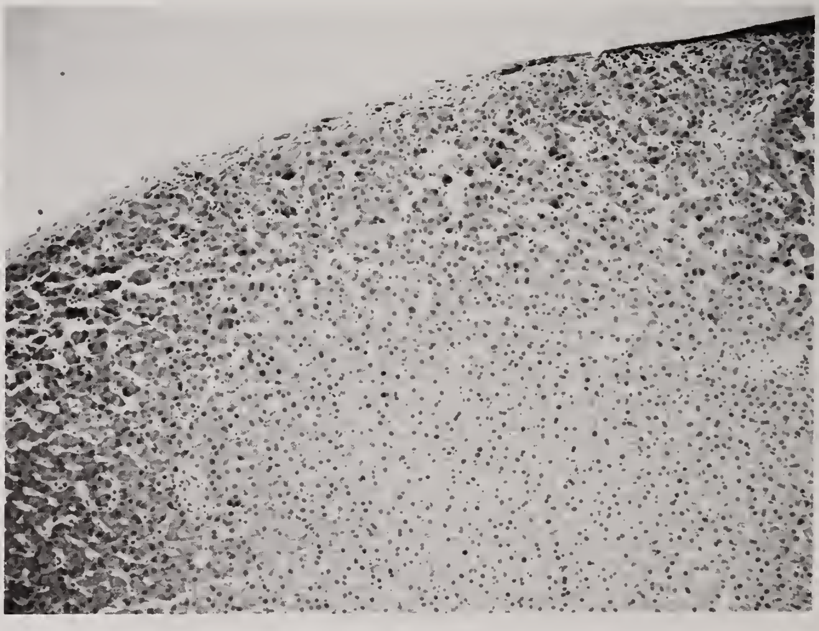

FIG. 1. Livery biopsy showing thin, intact visceral peritoneum (Glisson's Capsule). Hematoxylin and eosin stain, × 88.

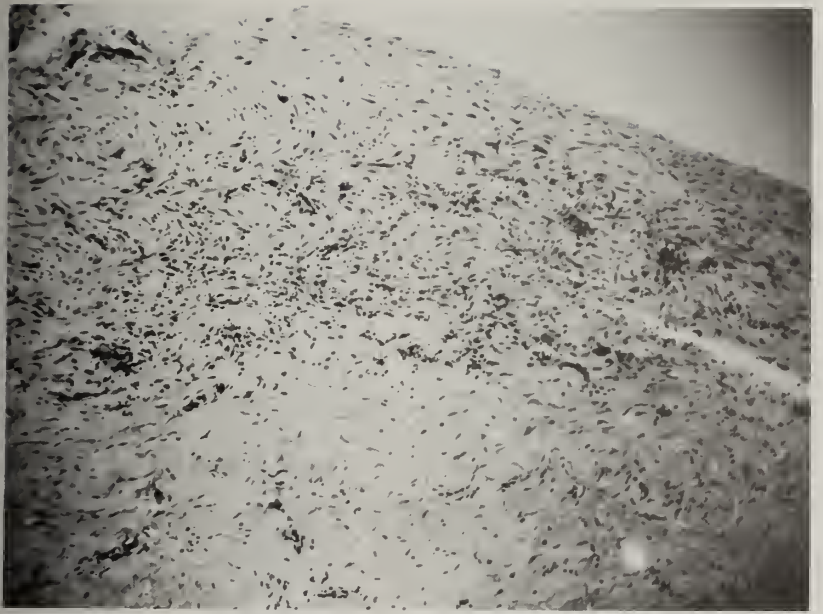

FIG. 2. Parietal peritoneum showing fibroblastic proliferation, mild chronic inflammatory cell infiltration, and collagenization of the deeper portions. Same magnification as Fig. 1 (hematoxylin and eosin stain, × 88).

pericarditis and unexplained pleuritis lends some weight to this speculation. Against this, however, is the absence of inflammatory changes in the liver capsule (visceral peritoneum), for if protracted renal failure is indeed a cause of peritoneal inflammation one would expect both visceral and parietal surfaces to be similarly involved. Furthermore, until sterile peritonitis with exudative ascites is noted in hemodialysis patients who have not had prior peritoneal dialyses, it would be hazardous to attribute this syndrome to renal failure per se. Finally, unlike the experience of Gutch et al[4] our patient eventually improved, lost all his ascites and at the time of this writing is doing very well on home dialysis.

Summary

A 34-year-old man with end-stage renal failure is described who developed massive and disabling ascites during maintenance hemodialysis treatment. An extensive diagnostic work-up including exploratory laparatomy revealed non-specific inflammatory changes on peritoneal biopsy. The ascites eventually cleared after months of aggressive hemodialysis with ultrafiltration and a tight abdominal binder. The findings suggest that this syndrome is related in some way to the previous peritoneal dialyses rather than to the protracted uremic state.

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Application of Thermography in Peripheral Vascular Diseases*

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Introduction

Thermography is a pictorial representation of infrared energy reflected by skin. It is a relatively new, simple, fast and noninvasive technique of measuring skin temperature photographically. Whereas a careful examiner can usually appreciate temperature variations as little as 1°C on two adjacent sites of skin surface at the bedside, thermography can be ten times more sensitive and is capable of detecting temperature difference as small as 0.1°C. The value of thermography in clinical medicine seems to be well established and extensive work has been done to evaluate its usefulness in breast cancer and metastatic disease.[1] It has also been reported to be valuable in evaluating cerebrovascular insufficiency,[2] pulmonary vascular disease,[3] angina pectoris,[4] coarctation of the aorta,[5] varicose veins,[6] thyroid nodules,[7] localization of hyperfunctioning parathyroid glands,[8] and localization of the placenta,[9] etc.

The purpose of this paper is to present some representative examples in the peripheral vascular field in which we found thermography helpful.

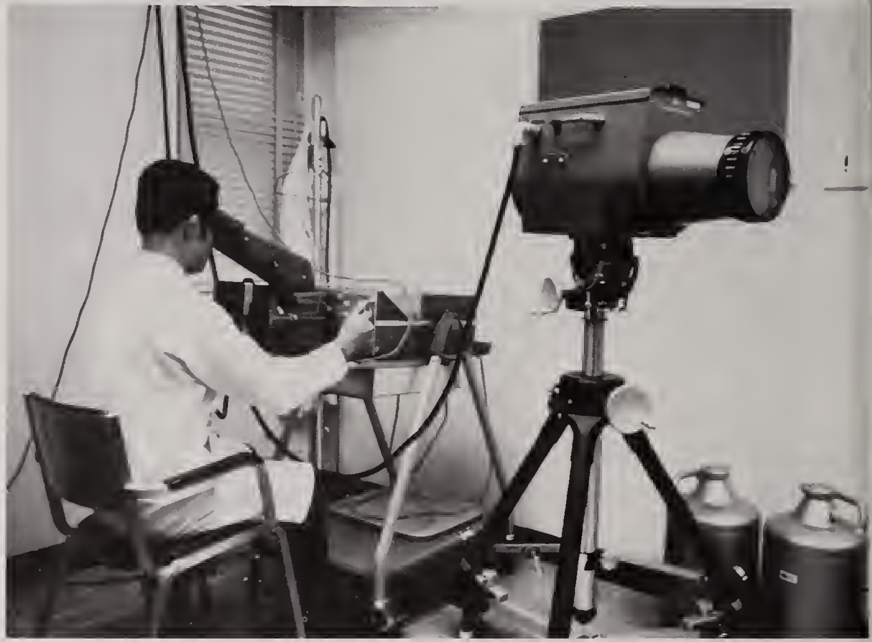

FIG. 1. AGA Thermovision.

Methods

The thermographic equipment used was an AGA Thermovision (Figure 1). The temperature of the room was maintained around 70° ± 2°F. Patients were brought in the room and their extremities were exposed to ambient room temperature for approximately 15 minutes by removing all clothing from the areas of interest in order to obtain thermal equilibrium. For two hours prior to examination, patients refrained from eating, drinking or smoking to minimize vasomotor activity as far as possible. In each case a detailed medical history was obtained and a physical examination performed.

Illustrative Cases

Case 1. R. S., a 52-year-old white man was admitted to George Washington University Hospital with a three week history of numbness, tingling, pallor of the left leg up to the thigh, of sudden onset. The patient gave a history of bilateral intermittent claudication lim-

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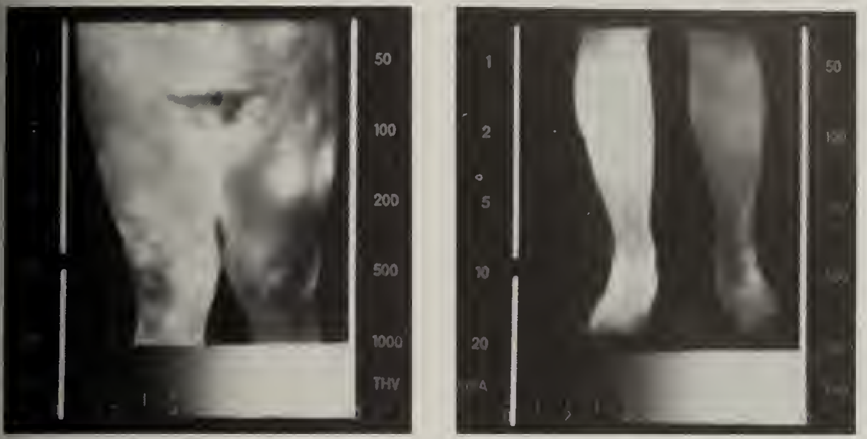

FIG. 2. Patient 1: Occlusion of left superficial femoral artery. Thermogram of anterior surface of lower extremities. Cool regions are thermographically dark; warmer areas are light gray or white. Note decreased temperature over the entire left lower limb.

ited to the calf muscles, precipitated by walking three to four blocks, of six to seven years duration. He had diabetes, gout, a past cerebral vascular accident, a myocardial infarction in the past, and had smoked two packs of cigarettes a day for 35 years. Physical examination showed a markedly obese man. Peripheral artery pulsations below the femoral artery were absent bilaterally. No ischemic necrosis or gangrene were present. Thermograms (Figure 2) demonstrated decreased temperature over the entire left lower extremity. Angiograms (Figure 3) confirmed the occlusion of the left superficial femoral artery at a point consistent with the thermographic pattern.

Case 2. A 59-year-old caucasian female had noted her right leg to be longer than the left since childhood. The patient denied a history of any preceding trauma or operative procedures. Close questioning elicited a history of easy fatigability of the right leg. On physical examination pertinent findings were: the blood pressure was 120/70, the right lower extremity was one inch longer than the left and the circumference of the right thigh was 1/8 inch greater than the left. No varicose veins or ischemic skin ulcers were present. The right femoral artery pulse was bounding and a grade 4 of 6 continuous murmur was heard over the right groin and medial aspect of the thigh. No other pulsatile masses were noted. The rest of the physical examination was unremarkable. Thermograms of the lower extremities (Figure 4) showed an obvious temperature difference, with the right leg 2°C warmer, substantiating the clinical impression of a femoral arteriovenous fistula. A femoral angiogram was suggested, but since the patient was asymptomatic she declined this procedure.

Case 3. N. S., a 62-year-old white woman, presented with typical Raynaud's Phenomenon of both hands of several years duration. The criteria were fulfilled that were set forth by Allen and Brown[10] for the diagnosis of primary Raynaud's Phenomenon. Causes of secondary Raynaud's were searched for and excluded. Except for a history of mild hypertension no

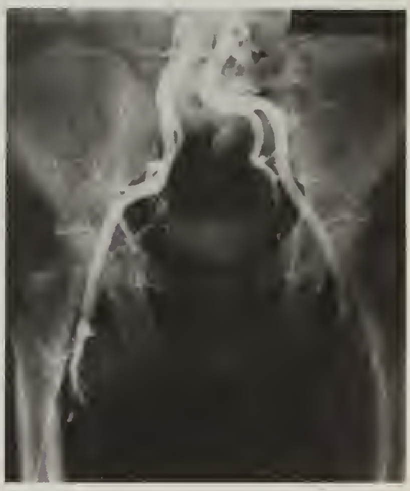

FIG. 3. Angiograms of lower extremities. Occlusion of left superficial femoral artery, corresponds with thermogram of figure 2.

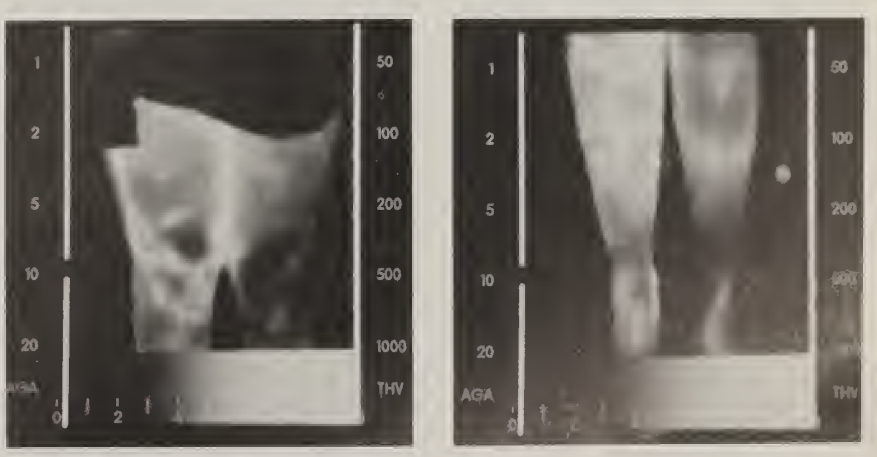

FIG. 4. Patient 2: Femoral arterio-venous fistula right side. Thermograms of anterior surface of lower extremities. Skin temperature over the right leg is 2°C warmer than the left.

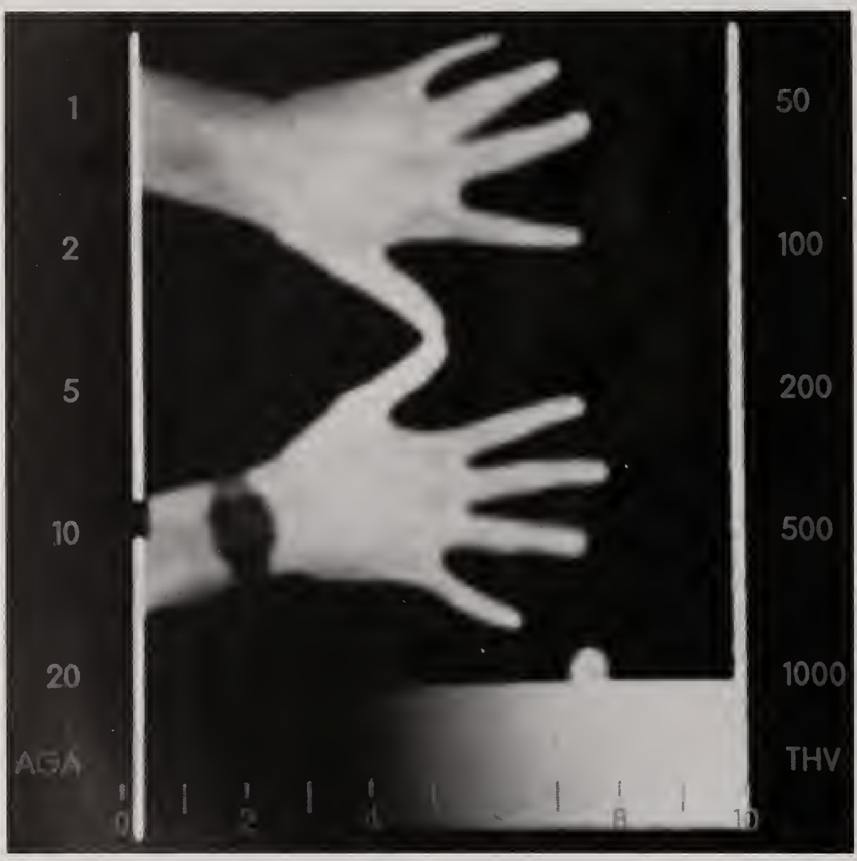

FIG. 5. Normal control. Thermograms of hands.

other systemic illness was apparent. Physical examination showed normal peripheral artery pulses and no ischemic necrosis of the hands. Thermograms of the hands (Figure 6) demonstrated that all fingers except the thumbs were cold compared with a normal control (Figure 5). A recently devised test[10] to substantiate the diagnosis of Raynaud's Phenomenon was performed. The patient's hands were placed in very thin disposable plastic gloves and immersed in an iced water bath for 60 seconds, after which the hands were removed from the iced water and the gloves discarded. Serial pictures of the hands were then made of the thermal changes. Figure 7 shows cold hands immediately after immersion and Figure 8 shows hands after complete rewarming. While in normal persons the hands completely rewarm in less than 20 minutes, patients with Raynaud's take substantially longer.

Case 4. M. D., a 30-year-old Negro woman, a housewife, presented with arthralgias, myalgia, pleuritic chest pain, dysphagia, weight loss and typical Raynaud's Phenomenon of both hands since 1968. On physical examination the only abnormal physical finding was acne vulgaris of the face. Peripheral arterial pulsations were normal. Pertinent laboratory work, including complete blood count, platelets, electrocardiogram, chest X-ray, lupus erythematosis cell preparations, antinuclear antibody studies, rheumatoid factor, and Coombs test were negative. Esophageal motility studies were consistent with progressive systemic sclerosis.

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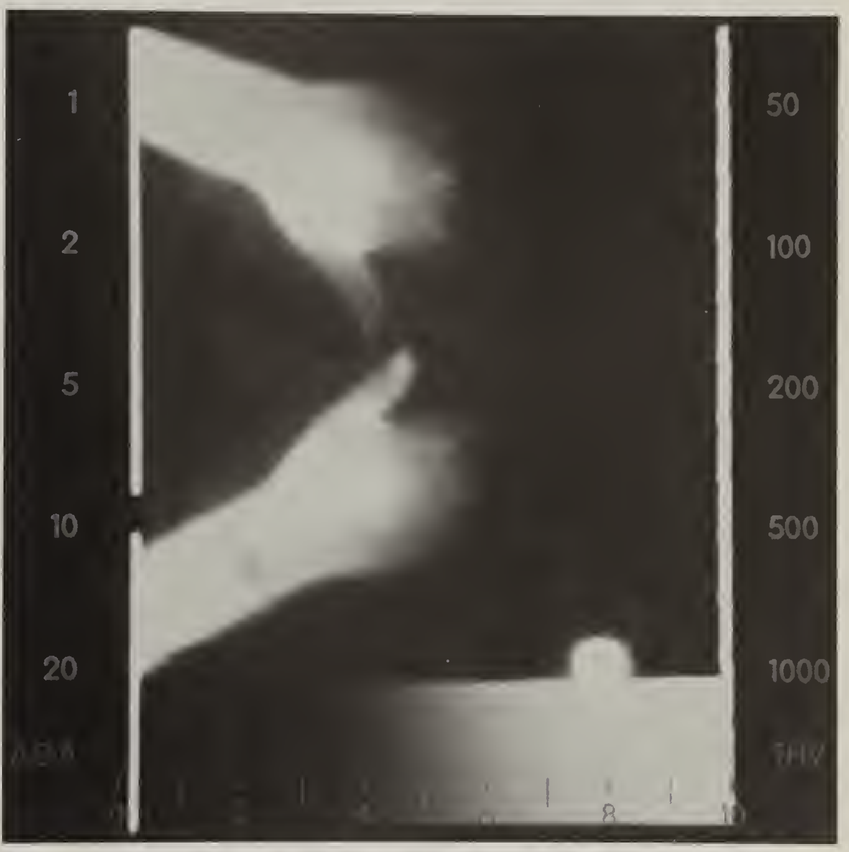

FIG. 6. Patient 3: Raynaud's Phenomenon. Thermogram of dorsal aspect of both hands showing cold fingers.

During the hospital stay, the patient developed pain in the posterior aspect of the right leg and thigh. Clinical examination showed tenderness in that area without a palpable venous cord. Deep thrombophlebitis was suspected and supported by thermography (Figure 9), which demonstrated a well defined linear area of skin of considerably increased temperature overlying the corresponding deep vein in the posterior aspect of the thigh.

Discussion

The detection of general or local body temperature abnormalities has been recognized by the ancients as a significant indication of disease. The human skin emits infrared radiation as a function of its temperature and emissivity.

The temperature of the skin is a result of a dynamic equilibrium between the heat gained by blood circulation and the conduction from inner parts of the body versus heat loss from its surface by radiation, convection and evaporation. Thermal changes from pathological processes are caused by one or more factors such as structural abnormalities of vessels, derangements of vascular control, changes in thermal properties of tissues and locally increased metabolic activities.

The infrared radiation is mainly concentrated at wave lengths between six and 15 micrometers. A display of area-by-area temperature differences

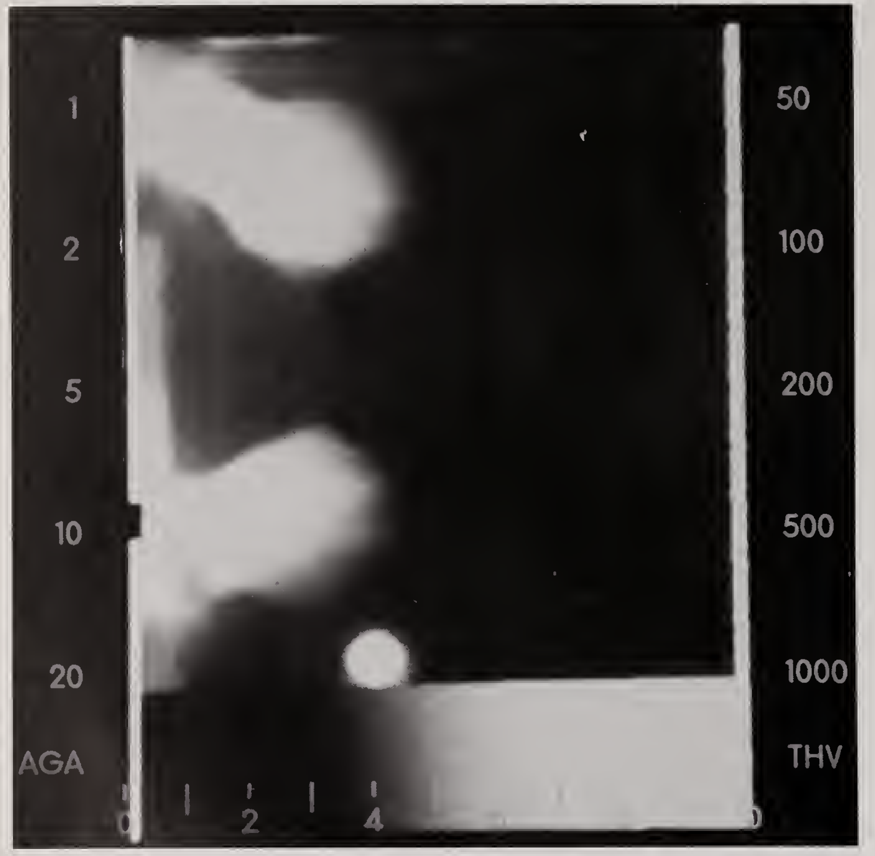

FIG. 7. Patient 3: Raynaud's Phenomenon. Iced water test. Thermogram of dorsal aspect of both hands immediately after immersion in iced water.

of various surfaces of the body obtained by a scanning technique is called a thermogram. The thermogram converts the perceived infrared radiation into an output demonstrated by a photograph, television, or cathode ray tube display. The actual temperature may be measured by comparison of the resultant image with a standard infrared source of known temperature. Most instruments can be set to detect differences in temperature of as little as 0.1°C.

It is important that a thermogram be performed in a room with controlled temperature, otherwise the reproducibility is variable and the results obtained may be misleading. The colder areas on the thermogram are usually represented as dark gray or black shades and the warmer areas as light gray or white. However, this standard practice of representation of shades can be reversed if desired.

Thermograms have been reported to reliably locate the anatomical site of the incompetent perforating veins in the leg in the patients with varicose veins. In 45 patients with varicose veins, Patil and co-workers[6] were able to localize the site of incompetent perforators in 94% of cases preoperatively by thermography. This is indeed a very helpful technique since success of surgery in the treatment of varicose veins depends on accurate preoperative localization of incompetent perforators both in the thigh and in the legs.

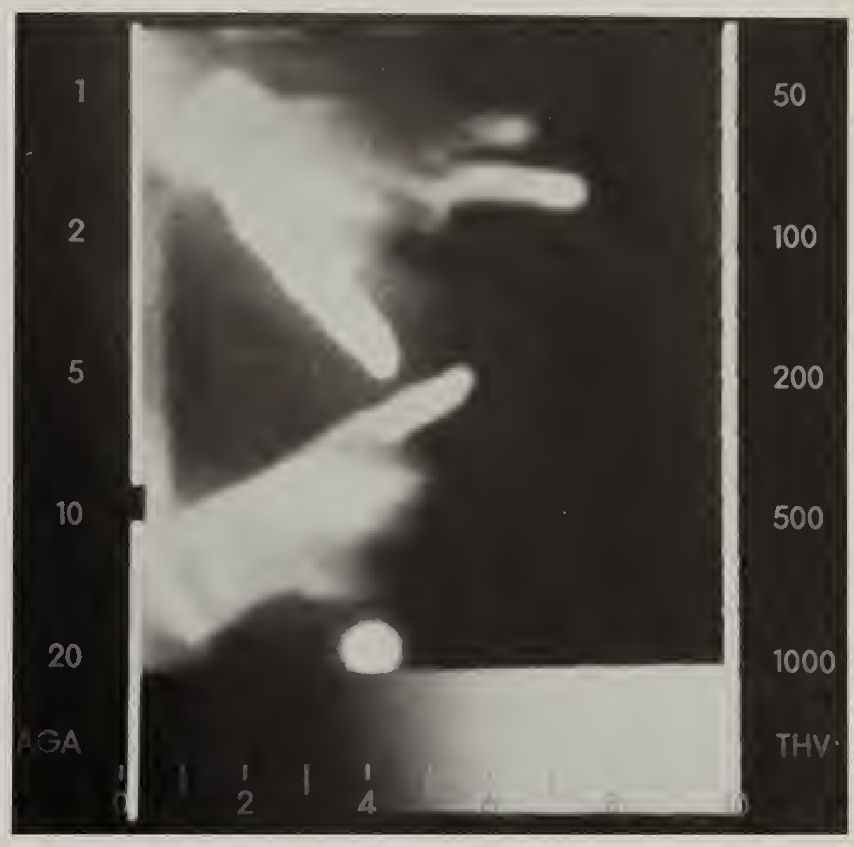

FIG. 8. Patient 3: Thermograms of both hands after rewarming for 20 minutes.

Thermography has been applied in the diagnosis of coarctation of aorta. Abernathy and colleagues[5] studied six children with unequivocal clinical evidence of aortic coarctation and 22 normal, healthy children. Thermograms of the diseased group had distinctly different patterns of thermal radiations from those of the normal subjects. Thermograms of patients with coarctation revealed heat emission patterns of collateral arterial blood flow, reflecting compensatory vascular adjustments which develop in response to the lesion.

Chucker and co-workers[10] have described thermographic observations in Raynaud's Phenomenon. Their study described 24 patients with Raynaud's disease, varying from 20 to 72 years of age, 20 women and four men with 51 normal control subjects. A photograph was made of the initial thermographic display of the hands. The hands were then immersed in an iced water bath for 60 seconds and serial pictures obtained in the rewarming period until complete recovery. Whereas in the majority of normal controls the hands returned to near the basal state in less than 20 minutes, patients with Raynaud's took a considerably longer time for recovery. These authors were unable to differentiate Raynaud's Phenomenon from Raynaud's disease as has been stated elsewhere in the literature.[11]

The usefulness of thermography as a

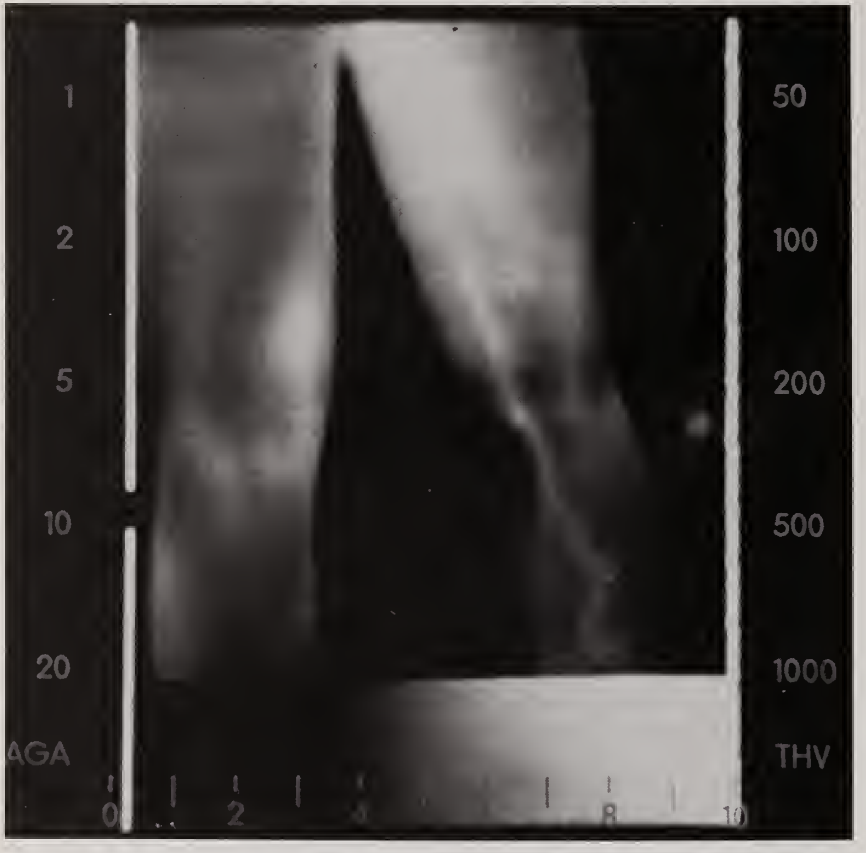

FIG. 9. Patient 4: Thrombophlebitis of right leg. Thermograms of posterior aspect of both lower limbs, showing increased temperature of the skin over the corresponding inflamed vein.

screening procedure in the evaluation of occlusive vascular disease is, however, limited. In a small series[12] of 15 patients with occlusive arterial disease of lower extremities, only eight showed good correlation between thermographic and arteriographic observations. In the remaining patients thermography was normal while the arteriographic picture was not. Normal thermograms were attributed to the development of good collateral circulation or only partial narrowing of vessels without complete occlusion.

Conclusion

Thermography provides a photographic representation of body surface temperature. It is a fast, simple, noninvasive technique free of radiation hazard. Its value in peripheral vascular diseases is discussed and some representative cases are presented.

Acknowledgment

The authors express their sincere appreciation to Miss Leslie Rowe for secretarial assistance in the preparation of this manuscript.

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A Statistical Study of Infants Born with Withdrawal Symptoms In the District of Columbia

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Abstract

Drug usage (particularly heroin usage) by expectant mothers can result in infants born with the withdrawal syndrome. Most of the research to date on the effect of drugs on the fetus and on the newborn infant has been qualitative. In order to obtain quantitative information on the problem of infants born with withdrawal symptoms, a survey was conducted of nine hospitals within the District of Columbia. The findings from the survey were of a rate of 4.0 infants born with withdrawal symptoms per 1,000 births in 1971 for four hospitals which provided these data; of a rate of 4.1 infants born with withdrawal symptoms per 1,000 births for the first four months of 1971 for these four hospitals; these could be compared to the rate of 5.4 infants born with withdrawal symptoms per 1,000 births for the first four months of 1972 for these same hospitals.

Among the seven hospitals in the survey which provided data for the first four months of 1972, there was a rate of 5.1 infants with withdrawal symptoms per 1,000 births.

The survey asked whether each hospital had a screening process in which mothers were queried prior to delivery about possible drug use. Five hospitals provided information. Three of these hospitals, accounting for about 37% of the births occurring in the surveyed hospitals for the first four months of 1972, responded that there was no uniform screening process.

Introduction

Most of the research to date on the effect of drugs on the fetus and on the newborn infant has been qualitative, rather than quantitative. Not the least of the problem, however, is that drugs taken illicitly, drugs given to an expectant mother, or drugs given as analgesics during childbirth may affect the fetus or resulting newborn infant.

Goodfriend, Shey and Klein[1] have reviewed the recorded cases of morphine addiction developed in utero. They emphasize that "morphine addiction is a phenomenon probably much more frequent than is realized and is no doubt missed because of lack of recognition of withdrawal signs from one to three days after birth." Presumably, they say, newborn babies diagnosed as addicted have also acquired tolerance, as otherwise they might have perished of asphyxia at birth. Withdrawal signs can occur in utero, as markedly increased fetal activity has been observed in the pregnant addict when beginning to crave a dose. It has also been noted that the newborn of addicted mothers who had their last dose ten days or more before delivery developed no withdrawal signs, suggesting that the addicted fetus may be cured in utero.

There are apparently differences of opinion with regard to the frequency or use and dosage of narcotics among pregnant women, and how close to delivery a drug must be taken to produce an effect on the newborn. Symptoms of withdrawal can include tremors, irritability, respiratory distress, hyper-activity, twitching, convulsions, vomiting, excessive weight loss, sneezing, yawning, chewing and sucking on the hands, watery stools and a shrill cry. Kahn, Newman and Polk, however, state that these symptoms are nonspecific and are difficult to express in quantitative terms[2]. Indeed, these symptoms are not unlike those associated with a number of other problems which may beset a newborn infant.

Most studies mention that withdrawal symptoms occur within 24 hours after birth. There is a difference of opinion on the best treatment for this problem, and even on the mortality rate. In one study made on 38 newborn infants with symptoms of heroin withdrawal, there were no deaths and serious morbidity was confined to low birth weight and diarrhea[2].

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A rough survey of the literature on this problem has shown primarily articles of either general scope, or citation of experience within a specific institutional setting. No article has been found surveying experiences within two or more institutional settings over a period of time to permit statistical analyses of trends.

Methods and Materials

In order to obtain quantitative material on the problem of infants born with withdrawal symptoms within a geographical boundary, a survey was initiated in May 1972 of nine hospitals within the District of Columbia. All hospitals were included in *Listings of Health Care Institutions* by the American Medical Association (1971).

The survey instrument was a letter addressed by name to, in most cases, the Chief of the Department of Pediatrics for each hospital. Information requested included: (1) the number of infants born with withdrawal symptoms and the total number of infants born, by month, for the first four months of 1972; (2) whether it would be possible to obtain the same information for 1971; (3) whether the information supplied could be subdivided according to race of mother (White, Negro, other) and residence of mother (District of Columbia, Maryland, Virginia, other), (4) whether the hospital had a screening process in which mothers were queried prior to delivery about possible drug use and, if so, what proportion of the mothers who delivered in the hospital were queried, and (5) of the mothers queried, what proportion received a query during a prenatal visit rather than at the time of delivery.

Comments from the physicians on the collection of statistics of this nature either within their own hospitals, the District of Columbia or more generally were also solicited.

Provision was made in the survey for follow-up letters and telephone calls should the initial inquiry fail to obtain an answer. No follow-up was made, however, if the information supplied was not in the desired form, unless the total number of births for a hospital for 1971 or for the first four months of 1972 was not provided. This was because it became evident that most medical records departments and/or physician's contacted did not have the desired information readily available and the burden on hospital staff to collect and compile the information in the desired form was unrealistic.

Results

Of nine hospitals contacted, some information was received from seven for a response rate of 78%. One of the hospitals contacted refused to supply any information and the other hospital did not respond to the survey at all, even after repeated attempts to obtain information.

As can be seen in Table 1, information supplied in response to the query was quite variable. No hospital queried had on hand or ultimately supplied all of the information requested. It seemed to be particularly difficult for

TABLE 1: Number of infants born with withdrawal symptoms*, number of births and rate of infants born with withdrawal symptoms per 1,000 births, according to month of birth: District of Columbia General Hospital, January 1971-April, 1972

	Total		Month of Birth											
Year of Birth	Year	Jan to Apr	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
1971														
Infants with withdrawal symptoms	44	17	3	5	6	3	6	3	2	1	2	5	4	4
Number of births	4051	1392	380	338	352	322	357	318	342	303	365	341	272	
Rate per 1,000 births	10.9	12.2	7.9	14.8	17.0	9.3	16.8	9.4	5.8	3.3	5.5	14.7	14.7	11.1
1972														
Infants with withdrawal symptoms	xxxx	10	2	6	1	1	xx	xx	xx	xx	xx	xx	xx	xx
Number of births	xxxx	1106	337	275	265	229	xx	xx	xx	xx	xx	xx	xx	xx
Rate per 1,000 births	xxxx	9.0	5.9	21.8	3.8	4.4	xx	xx	xx	xx	xx	xx	xx	xx

* Underestimate because of some missing charts.

the hospitals to separate mothers according to residence. In regard to the item on the screening process, information was received from five hospitals.

For 1971, the four hospitals which provided data on the number of infants born with withdrawal symptoms accounted for approximately 13,591 of the 25,024* births occurring at the nine hospitals included in the survey (or for about 54% of these births). The recorded number of infants born with withdrawal symptoms at these hospitals in 1971 was 55†, for a rate of 4.0 infants born with withdrawal symptoms per 1,000 births. The overall rate for 1971 for these hospitals was lower than the rate which occurred for these hospitals for the first four months of that year. For the first months of 1971, these hospitals experienced a rate of 4.1 infants with withdrawal symptoms per 1,000 births (or 19 out of some 4,624 births).

For the first four months of 1972, the same four hospitals accounted for about 3,917 births out of some 7,225 births occurring at the hospitals included in the survey (or for about 54% of these births). 21 infants were born with withdrawal symptoms at these hospitals during this time for a rate of 5.4 infants with withdrawal symptoms per 1,000 births. This rate was only slightly higher than that shown for these hospitals in 1971 during an identical time period.

Among the seven hospitals in the survey which provided data for the first four months of 1972, there were 32 infants with withdrawal symptoms out of some 6,257 births. This resulted in a rate of 5.1 infants with withdrawal symptoms per 1,000 births.

The majority of infants with withdrawal symptoms were born in the District of Columbia General Hospital, the only city operated hospital in the survey. Table 1 shows, for the District of Columbia General Hospital, the data for 1971 and the first four months of 1972, subclassified according to calendar month.

As can be seen in Table 1, at the District of Columbia General Hospital for 1971 there was a rate of 10.9 infants born with withdrawal symptoms per 1,000 births. By month, there appeared quite a variation in the rates with a high of 17.0 infants with withdrawal symptoms per 1,000 births in March to a low of 3.3 infants with withdrawal symptoms per 1,000 births in August. For the first four months in 1971, there were 17 infants born with withdrawal symptoms out of some 1,392 births—a rate of 22.0 infants with withdrawal symptoms per 1,000 births. For a comparable period of time in 1972, there were 10 infants with withdrawal symptoms out of some 1,106 births, resulting in a somewhat lower rate, 9.0 infants with withdrawal symptoms per 1,000 births.

Although the intent of the letter addressed to the hospitals was to obtain both numerator and denominator data according to race and residence of mother, these data were not provided. In most cases, the hospitals providing data according to these characteristics supplied the information only for infants born with withdrawal symptoms. Thus, it is not possible to construct rates other than those shown.

Four hospitals provided data on the race of infants born with withdrawal symptoms in 1972. All 14 infants born with withdrawal symptoms in these hospitals were Negro. Two hospitals provided residence data on mothers of these infants. For all five of the infants born with withdrawal symptoms in these two hospitals, the residence of the mother was in the District of Columbia.

In regard to the item in the letter on whether a hospital had a screening process in which mothers were queried prior to delivery about possible drug use, of five hospitals providing information to this item the response of three was that there was no uniform screening process. These three hospitals accounted for about 37% of the births occurring in the surveyed hospitals for the first four months of 1972.

One of the two hospitals which responded affirmatively to whether a screening process was present stated that it was fairly uniform, at least by the time of labor. The other hospital indicated that virtually all staff mothers were queried about drug usage—either through attendance at the prenatal clinic (about 80%) or just prior to labor (20%). However, few private patients were queried. These two hospitals accounted for approximately 23% of the births occuring in the surveyed hospitals for the first four months of 1972.

Discussion

It is quite evident that there are a number of limitations to obtaining reliable and valid data on the number of infants born with withdrawal symptoms within a geographical boundary. These limitations include nonspecific symptoms which may not be recognized as pertaining to drug withdrawal (therefore no record of such an occurrence is made), inadequate staffing of medical records departments, incomplete records on infants born with withdrawal symptoms and data retrieval systems that are outmoded and do not lend themselves to statistical analyses. In addition, there seems to be a serious error of omission in the prenatal programs conducted by some hospitals in the District of Columbia and in information obtained from expectant mothers just prior to delivery. This error of omission concerns querying an expectant mother as to her drug use and informing her of the possible effects on her baby.

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* The number of births at these hospitals for 1971 and 1972 was compiled from information supplied on return letters or by means of a phone call to the hospitals. This number may differ from that generated by the District of Columbia Health Department.

†Represents a known underestimate since at D.C. General Hospital it was not possible to locate all records.

Data provided in response to this survey do not allow a statement on the proportion of mothers delivering in the surveyed hospitals who are queried about drug use prior to actual delivery nor, for those mothers who are queried, the proportion queried at the time of a prenatal visit as opposed to just prior to delivery. At least three of the nine hospitals included in the survey—accounting for about 37% of the births in the surveyed hospitals—stated that there was no uniform screening process.

At least for the sake of the infant, if not the mother, it would seem that a query directed to *all* expectant mothers about drug usage would result in a lessening of morbidity and mortality occurring at the time of childbirth; at least that morbidity and mortality associated with withdrawa from drugs.

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Peutz-Jeghers Syndrome
Case Report*

EDWARD E. CORNWELL, JR., M.D., F.A.C.S.†, MASUD HOMAYOUNI, M.D.‡
AND FRANCES BLACKWELL, M.D.§

Introduction

The Peutz-Jeghers Syndrome was first reported by Peutz in 1921 and further elaborated upon by Jeghers in 1949. The syndrome is characterized by gastro-intestinal polyposis with melanin spots of the lips, digits and buccal mucosa. (Fig. 1) The condition is familial and is transmitted by a simple Mendelian dominant gene. There are conflicting views as to the frequency of malignant change and the true histological nature of the polyps found in patients with this condition. The patients encountered with polyposis due to Peutz-Jeghers variety were first reported to have small bowel involvement. As more cases were found the polyps have been noted to occur from the mouth to the anus. It is also noteworthy that in Peutz's original cases one of his patients had nasal polyps.[2-3] Malignancy has been reported sporadically in patients with Peutz-Jeghers Syndrome. These malignancies have been found in the stomach, duodenum, small bowel, and the colon.[4] An unusual case of carcinoma of the stomach with metastases to lymph nodes in a case of Peutz-Jeghers Syndrome has been reported by Payson.[5] The malignant potential for small bowel polyps is low according to Dormandy.[1]

The typical patient with Peutz-Jeghers Syndrome usually presents with signs of small bowel obstruction caused by intussusception. Anemia has been reported in one-third of the cases. A conservative approach to eradication of the polyps of the small bowel is indicated because of the low malignant potential[1], though a more aggressive approach is indicated when polyps are found in the stomach, duodenum and the colon. The occur-

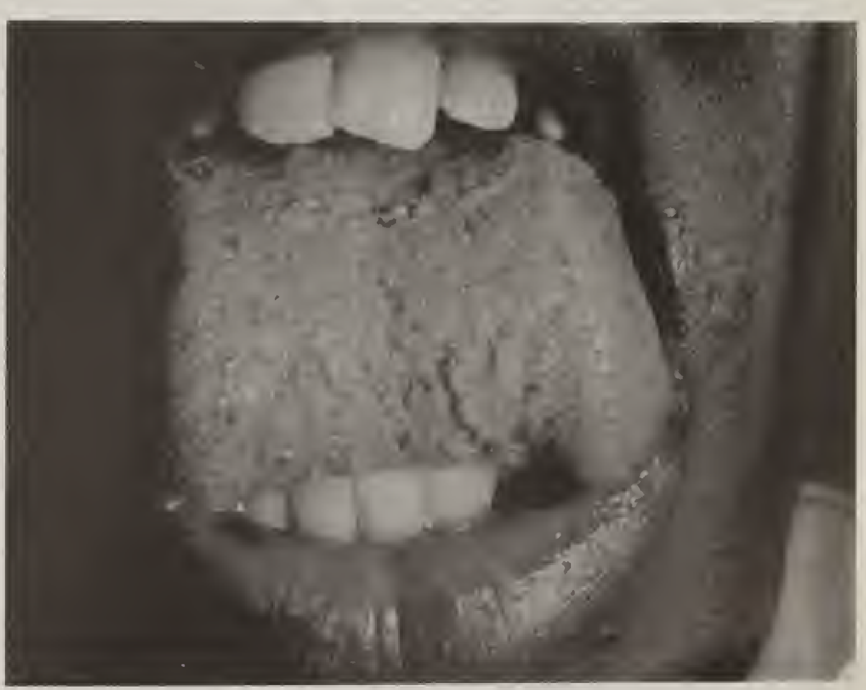

FIG. 1. Pigmentation of the lip and the circumoral region.

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rence of ovarian tumors with the Peutz-Jeghers Syndrome is well documented.[6-9] The Peutz-Jeghers Syndrome is frequently associated with other congenital abnormalities, including Polycystic disease of the kidney. These patients usually have an abnormally long "Y" chromosome.[7] Other congenital defects such as cardiac defects, aneurysms of the cerebral vessels, cysts of the liver, spleen, lungs and urinary bladder polyps have been noted in patients with Peutz-Jeghers Syndrome.[8] Documentation of sickle cell anemia or sickle cell trait in Peutz-Jeghers Syndrome has not been previously alluded to in the literature, and its significance may be only casual in that a significant number of black patients carry the congenital defect of sickle cell disease and trait. More important than the relationship of sickle cell anemia to intestinal polyposis is the probability that the true nature of the anemia may be overlooked in a patient with abnormal hemoglobin if the intestinal tract is not examined radiologically.

When one encounters such a patient with Peutz-Jeghers Syndrome it is well to keep in mind that numerous other congenital defects may be present. There has been considerable controversy as to the true histological nature of the polyps encountered in the syndrome. The older literature initially described these polyps as being adenomatous polyps, however it is generally agreed now that the polyps are hamartomatous.[4-9] The melanin deposits of the skin and the buccal mucosa are non-specific and have been previously described.[7]

Case Report

A 25-year-old black male was admitted to the hospital on 11-27-67 because of easy fatigability, weakness and anemia. Physical examination revealed the typical mucocutaneous pigmentation of Peutz-Jeghers Syndrome with the pigmented areas ranging in size from 1-3 mm. The lips, the nasolabial folds, nostrils and eyelids showed the typical pigmentation. Pigmentation was also noted at the ends of the fingers but not the toes. There was marked pigmentation of buccal mucosa. It was also striking that the patient appeared much younger than his stated age of 25 years. Physical examination otherwise was essentially unremarkable. The patient was sigmoidoscoped and several polyps which appeared grossly to be pedunculated adenomatous polyps were noted at 10 cm., 15 cm., and 22 cm. The hemoglobin was 9.6 gm., hematocrit was 34%. Reticlocytes 6.2%, Serum Iron 35 mg., Serum Iron Binding Capacity 398 mg., and A-S hemoglobin was demonstrated an electrophoresis.

(Figure 2.) On 12-7-67 all polyps within the view of the sigmoidoscope were excised and numerous mucosal excrescences were cauterized. Barium enema confirmed the presence of polyps throughout the colon. Upper Gastro-intestinal series and small bowel series were normal. The patient had selective mesenteric arteriography which suggested a blush in the region of a polyp in the cecum. On 12-14-67 the patient has a colectomy with ileoproctostomy, leaving approximately 10 cm. of rectum. At the time of surgery the stomach and the entire small bowel were palpated for evidence of polyps. No polyps were found except in the terminal ileum which was resected along with the colon. Postoperatively the patient did very well. He was discharged on the 10th postoperative day and has continued to do well. An effort was made to examine other members of his family who were reported to be asymptomatic. Two members of the family were contacted but refused examination (Fig. 2, 3, and 4).

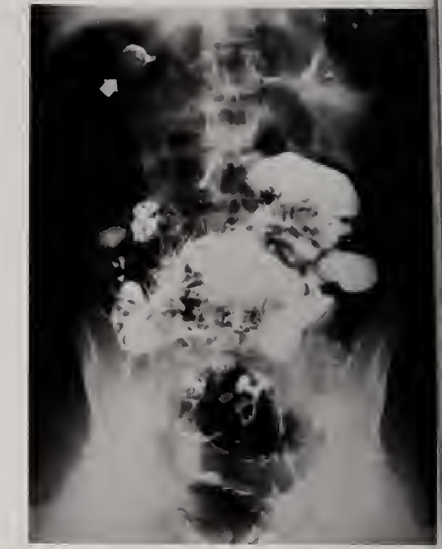
FIG. 2. Large pedunculated polyp of colon.

The specimen submitted for pathological examination consisted of 4 colonic polyps, a polyp of the terminal ileum, the entire colon, the appendix, and a 7 cm. segment of the terminal ileum. The mucosa of the colon, especially in its distal portion, was carpeted with innumerable polyps ranging in size from minute pinhead size mucosal excrescences to large 2 X 1 cm. pedunculated polyps. Five small polyps were present on the mucosa of the ileocecal valve. None of the polyps demonstrated ulceration or evidence of malignant degeneration grossly.

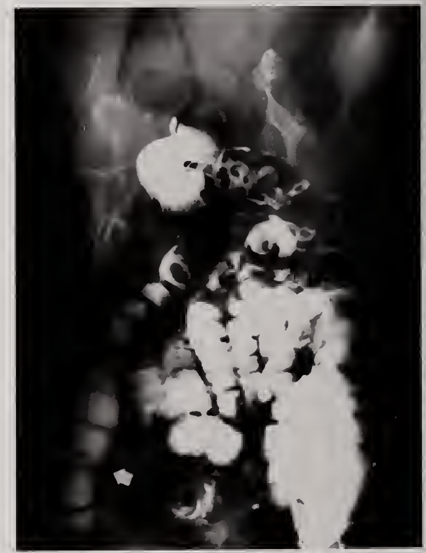
FIG. 3. Polyps of varying sizes of colon.

Microscopically, the tumors appeared to be adenomatous polyps demonstrating a central supporting connective tissue stroma with a muscularis mucosa covered by an almost normal appearing mucosa. The component cells were tall columnar and generally deeper staining than the normal mucosal epithelium with absence of mucus formation in many areas. Microscopic evidence of malignancy was lacking in all polyps examined. The ileal polyps presented an essentially similar histological picture, except the base of the lesion was covered by normal ileal type of mucosa. No Paneth cells or bands of smooth muscle fibers were present.

Discussion

Peutz-Jeghers Syndrome is one of the genetically related diseases of the gastro-intestinal tract with mucosal and skin pigmentation. The incidence of malignancy is low but has been reported sporadically. The disease more commonly presents with signs of obstruction and anemia. A conservative approach is warranted in treating the small bowel lesions because of the low malignant potential.

The gastro-intestinal polyps of Peutz-Jeghers Syndrome are thought to be hamartomatous malformations[4] composed of a mixture of tissues indigenous to the bowel wall. In this regard, they are non-neoplastic and therefore are not premalignant. The polyps of the present case however, can not be histologically differentiated from the common neoplastic adenomatous polyps of the large bowel.

If it is accepted that the typical circumoral and mucosal pigmentations, together with polypoid adenomatosis of the gastro-intestinal tract constitutes Peutz-Jeghers Syndrome, then it must be assumed that the histogenesis of the gastro-intestinal lesions varies in different cases, the polyps being hamartomatous in some patients and true neoplasm in others; as in the present case.

The low malignant potentiality of the small bowel lesion then implies a low tendency for this portion of the gastro-intestinal tract to develop carcinoma. Possibly the environment of the small bowel is not conducive to, or even counteracts, development of malignancy.[8] Of course, it is possible that in this case the pigmentation is unrelated to gastro-intestinal adenomatosis. This seems most unlikely in view of the clinical picture, typical pigmentation in conjunction with polypoid adenomatosis of the small and large bowel.

Multiple congenital defects have been reported in patients with Peutz-Jeghers Syndrome. The relationship to sickle cell anemia or sickle cell trait may not be significant, but in any patient it is important to assess the true nature of the anemia. The patient in this report tolerated surgery well, gained weight and is no longer anemic.

Summary

The Peutz-Jeghers Syndrome is characterized by mucocutaneous pigmentation and intestinal polyposis. The disease is transmitted by a Mendelian dominant gene. The kindred of such a patient should be examined. The polyps may be hamartomatous or adenomatous polyps. The disease may present with obstruction or anemia. Malignancy when found rarely involves the small bowel, and a conservative approach should therefore be used in treating the small bowel polyps. Malignant change in the stomach and duodenum has been occasionally reported. The Peutz-Jeghers Syndrome is frequently associated with other congenital abnormalities.

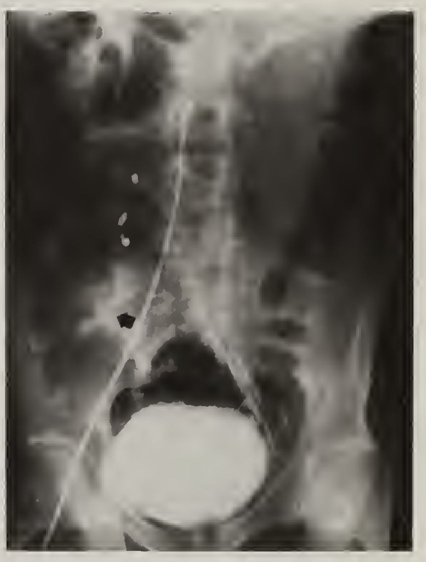

FIG. 4. Blush on arteriography in region of polyps of cecum.

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special articles

F-Stop, Anyone?

JOHN M. KESHISHIAN, M.D.*

The other day I saw an advertisement in one of the national magazines describing the "last word" in photographic equipment. A sort of Rube Goldberg concoction; an old bellows-type camera cum tripod which had been fitted up with some of the latest and snazziest features—kind of like a Model-A Ford with a supercharger. This, all to impress the modern shutter-bug with the obvious advances in today's cameras.

But it occurred to me that many of my shutter-bug physician friends possess the ultimate in camera equipment. You name it and they have it—the cost be damned, need it or not. Whatever the occasion demands, they have exactly the right piece of equipment for that particular situation. Never mind that they do not always know how to use it, but it is always available and impressive at the beach, conventions, receptions or weddings (where the hired pro goes bananas because Doc's flash triggers his strobe heads and ruins everything!).

Even at this very minute, some of my remaining friends are cranking up for the spring meetings overseas, San Francisco or wherever. The equipment is being tenderly readied, the lenses are polished and everything is in first-class order. Or is it?

Have the lenses been checked? Has the flash synch been checked out? Is the film winding properly on the spool? Do batteries need to be changed?

But, o.k., let us stipulate that everything is in shipshape order and our doctor friends are good, advanced stage, amateur photographers; that is, when it comes to getting the equipment together and taking the photograph itself. This they have down pat—it is almost reflex-like with them. They have the right lens, the right angles and the composition is second-nature to them.

But what happens when they come back and it is time for "Show and Tell"? Now, understand, we are not talking about the home movie fiend, or the "I-do-my-own-developing-and-printing-in-black-and-white" nut, but just the ordinary run-of-the-mill 35mm color slide commando (like me, if you please).

Well, Clyde Efstop, M.D., who has spent around $1,000 on his equipment (wholesale, of course, and from Hong Kong yet!), has just gone out to buy a batch of good fast film. He plans to have it processed by a large cut-rate firm whose advertisements can be seen in every issue of the Sunday magazine section. After processing, he projects the slides on the dining room wall with his bargain slide projector. The results, as we may guess, don't always impress the neighbors and somehow turn off dear wife, since she will swear that she was not jaundiced when the photos were taken (pictures don't lie) and that the 8 x 10 prints that he ordered of her are unspeakably bad. These, of course, are discarded before Mama and neighbors see them.

Within a few days, Dr. Efstop advertises his equipment in the Riker magazine as being available for the first reasonable offer and describes his equipment "like new".

Now, maybe I have overdone it, but what a way to lead into some suggestions.

First, do not buy film just because the price is right. Stick to one type of film; the type that you know best and the type that will get consistently good results. Even though I own stock in the Eastman Company, I must champion Kodachrome II as probably the finest all around film. Kodachrome II is a daylight reversal type film which is forgiving for at least 1½ stops in either direction and is remarkably consistent from batch to batch. It works well with flash fill-in to brighten up the dark shadows and is an excellent film to use for night flash shots. If we all followed the directions on the piece of paper that accompanies the film, we probably would not need to use the light meter, except under certain circumstances. But being addicted to the light meter, we do.

One small tip. If you do not have a light meter and are worried about the exposure to use, a general rule-of-thumb is, in good bright sun with the camera set at f-16, the speed of the shutter should be one over the ASA. That is to say, Kodachrome II has an ASA of 25. In bright sunlight at f-16 the shutter should be set at 1/25. Therefore at f-11, it would be 1/60 and at f-5.6, it would be 1/125. This applies no matter what type of film you use, as long as you remember that one over the ASA at f-16 is a safe setting to use.

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Be smart. Buy 36 exposures instead of 20 and bracket your shots. If your light meter tells you that a certain exposure is called for, shoot one under and one over on either side of the exposure. One of the three should be perfect, and it may not be the one from the light meter.

Remember, the cheapest commodity is the film. If you had to fly back to that same location to get that same shot, assuming it still existed, just think of how much it would cost you when contrasted with one or two extra shots and one or two extra rolls of film. If you are an avid photographer, plan on one to two rolls of film a day. Do not go short, hoping to economize. You'll always find something that ought to be photographed and find yourself out of film. There may not be any around.

Now on the subject of buying film, let me recommend this to you. In photography magazines you'll see advertisements for film plus mailers. Look them over carefully. I have dealt with one organization in New York for over ten years (Name on request). I buy Kodachrome II film and processing bags from them at a discount, and so can you! The exposed film is placed in the mailers, dropped in the mailbox and sent to the nearest Eastman Kodak processing plant and returned to your office. If you depart with 20 rolls of film and 20 processing bags, you don't have to be a genius to figure out that mailing the exposed film in San Francisco to the processing plant nearest home insures that the slides are waiting when you get home. Clever, no? You can also do this from Europe or most anywhere. A few pennies extra for stamps won't hurt.

On the subject, you can buy film in Europe, but the processing is usually included. Go ahead and get it. Kodachrome II is Kodachrome II everywhere; Eastman Kodak will honor the processing in this country.

Projecting slides on the living room wall is a hell of an injustice to the slides. First of all, the living room wall will absorb a lot of the color and possibly reflect some unwanted tints. Best you get a good screen, a lenticular screen, of course, is about the finest that money can buy. Make sure your projector is at right angles and on the same level as the screen. If you angle it from one side to the other or up and down, you will get some interesting effects which you hadn't planned on.

As to the projector, if you've got the gall to spend $1,000 on a camera, but haven't got the heart to spend a commensurate amount of money for an excellent slide projector, they you might as well go out and but a second-hand Brownie. Your slide projector can only be as good as its lens.

For example, a cheap projector most likely contains a poor quality lens. These lenses have two serious defects known as chromatic and spherical aberration. Those fancy terms are used to indicate that the lens is probably uneven and is of such low quality glass that the colors are altered, or something like that. But if you have one of the better projectors, such as the Carrousel, there'll be no problem.

One of these days soon we will have a follow-up article on some other aspect of photography for doctors. Meanwhile, if you have any questions, send them in to the Medical Annals Editor and we'll try to answer them for you.

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PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

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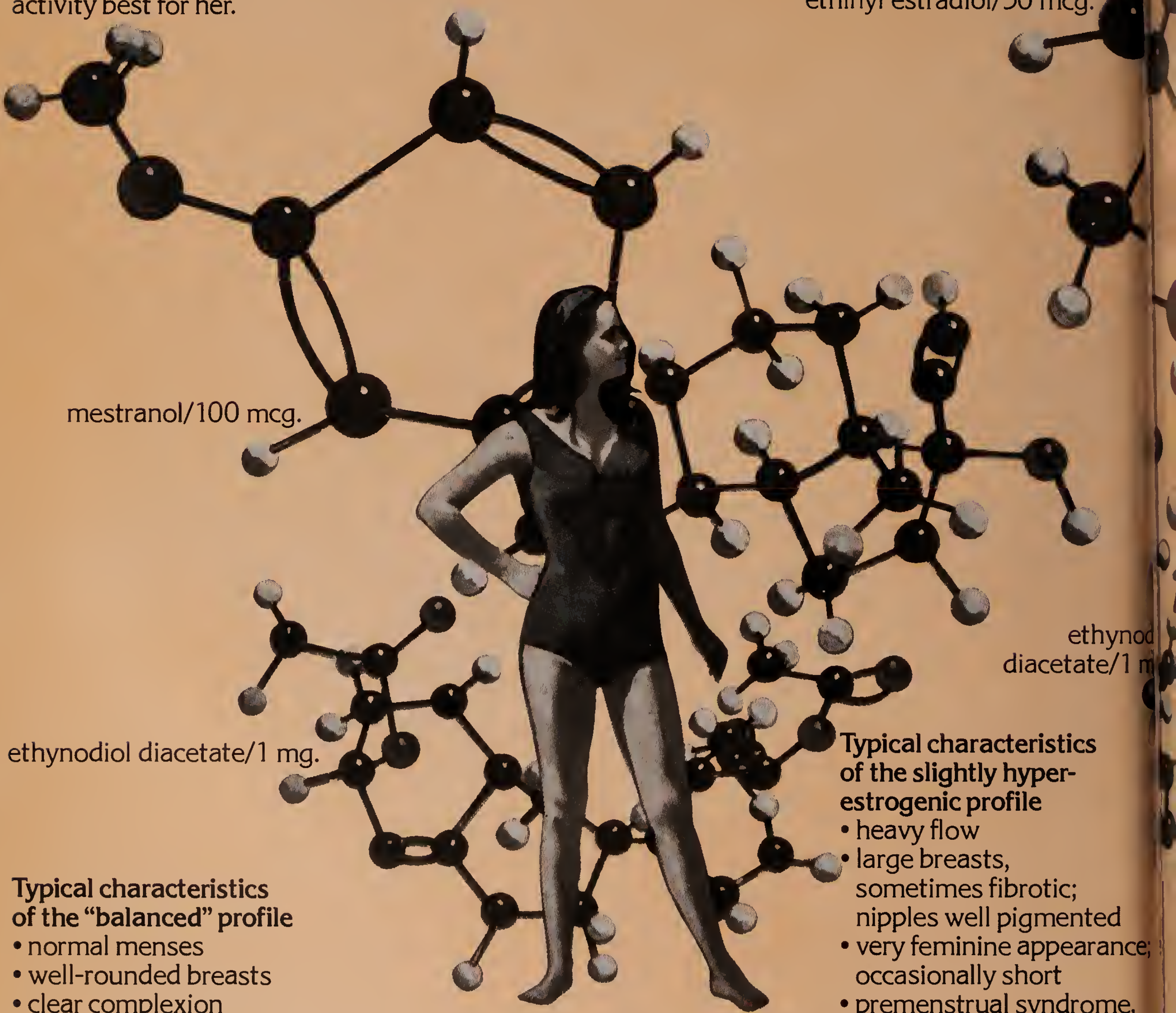
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ethynodiol diacetate/1 mg.
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Typical characteristics of the "balanced" profile
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Each white tablet contains: ethynodiol diacetate 1 mg./mestranol 0.1 mg.
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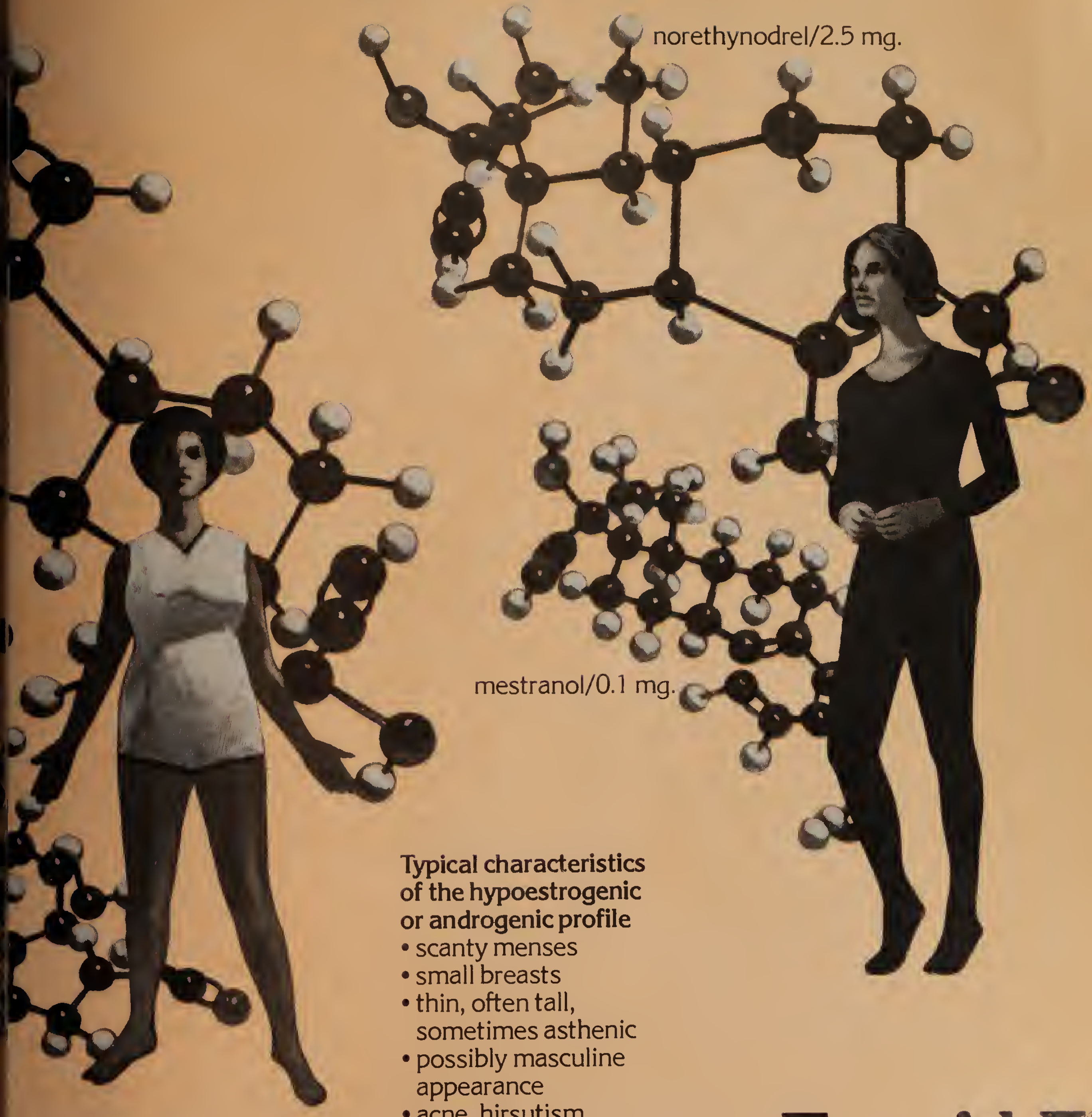
This formulation, which has less estrogenic activity and a moderate progestogen dominance, may be a good beginning.

For brief summary of prescribing information, please see next page.


norethynodrel/2.5 mg.
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Each white tablet contains:
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Actions—Ovulen and Demulen act to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen and Demulen depress the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note—Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations pre-existing uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967. **2.** Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. 2:193-199 (April 27) 1968. **3.** Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. 2:651-657 (June 14) 1969. **4.** Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Amer. J. Epidem. 90:365-380 (Nov.) 1969.

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Indication—Enovid-E is indicated for oral contraception.

The *Special Note, Contraindications, Warnings, Precautions* and *Adverse Reactions* listed above for Ovulen and Demulen are applicable to Enovid-E and should be observed when prescribing Enovid-E.

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Current Diagnosis and Treatment 1973. MARCUS A. KRUPP AND MILTON J. CHATTON. Price, $12.00. Pp. 996. Los Altos, California: Lange Medical Publications, 1973.

A useful and helpful desk reference for the busy practitioner. As stated in the preface, this text is not intended to be used as a textbook of medicine, but with one thousand pages of clinical and diagnostic information it approaches just that.

This will be the 11th and last annual publication of Current Diagnosis and Treatment, as the publishers plan a biennial publication starting with this year's edition.

The current edition is very readable but as with any cookbook approach, it tends to oversimplify problems and solutions. A major source of irritation is the persistence of ancient formulas and preparations, and the maddening apothecary system for certain prescriptions. This is really a minor defect however, and credit must be awarded the editors for achieving a uniform approach of subject matter despite numerous authors.

The Table of Contents and Index are easy to read and comprehend, and in a working text of this type, this is obviously important.

Any busy physician will welcome Current Diagnosis and Treatment to his desk.

GEORGE A. BOINIS, M.D.P.C.

Pulmonary Reactions to Coal Dust. A Review of U.S. Experience. MARCUS M. KEY, LORIN E. KERR AND MERLE BUNDY, Editors. Price, $14.00. Pp. 215 with illustrations. New York: Academic Press, 1971.

The monograph presents a multidisciplined review of coal miners' pneumoconiosis in the U.S. and compares this experience with the well documented European and British findings. The editors represent government, the mine workers, and industry, so a balanced presentation is given.

The reader is brought through the historical aspects and types of coal mining, the evolution of our thinking on the relationship of coal mining to respiratory disease, and the development of legislation in the U.S. to protect the worker. The types of coal mines, length of exposure, occupation in the mine, and dust concentrations are correlated to incidence and extent of disease. A discussion is presented on dust control and there is a later section on instrumentation to monitor dust levels.

The bulk of the monograph contains several chapters on the clinical characteristics of coal workers pneumoconiosis, including symptoms, pathology, chest roentgenology, pulmonary function studies, and complications. Studies are presented comparing these characteristics among different mining communities, among miners with different jobs in the mine, and among noncoal miners who live in the same community. Difficulty in separating other respiratory diseases, such as bronchitis and emphysema, in populations with high cigarette consumption is discussed.

In ably presenting the data of the U.S. experience in this field the book points out the difficulties of establishing cause and effect in this type of respiratory disease. The brief criticism I have with this book is that, like many multi-authored works, there is a great deal of repetition which could have been eliminated. I believe the monograph would be of interest to physicians who treat respiratory problems in coal miners, industrial groups, those interested in industrial disease and its control, or anyone interested in the role of government in the prevention of such disease.

BERNARD GRAND, M.D.

Vectorcardiography in Congenital Heart Disease. R. CURTIS ELLISON, M.D. AND NORMA J. RESTIEAUX, M.B., CH.B. Price, $13.50. Pp. 209 with illustrations. Philadelphia: W. B. Saunders & Company, 1972.

Despite the excellence and value of this small volume, its readers will probably remain restricted in number and interest. The authors, Drs. Ellison and Restieaux, have written for the highly specialized group of physicians, dealing solely or primarily with the study of congenital heart disease in infants and children. They describe the results of their studies using the Frank Vectorcardiogram to estimate the severity of certain aspects of congenital heart disease.

The work is basically an extension and expansion of that begun in the Sixties by Dr. Paul Hugenholtz. Vectorcardiograms from infants and children with congenital heart disease are analyzed in a quantitative way and correlated with cardiac catheterization and surgical observations. Value judgments are based on these correlations. The method requires calculation and measurement of maximum spacial voltages, a tedious and time consuming task if one does not have a handy-dandy computer nearby.

The authors, after an initial introduction into their methods of Vectorcardiographic analysis, attempt to demonstrate how to derive the left and right spacial voltages. For the uninitiated, the description leaves much to be desired. Better diagrams would be of considerable value.

Following the chapters describing the Frank System Vectorcardiogram and its analysis, the authors then commence the clinical part of the book with a chapter on normal infants and children's Vectorcardiograms. They conclude with chapters on abnormal Vectorcardiograms and specific lesions. Good correlation is demonstrated between pressures and spacial voltages in congenital aortic stenosis and pulmonic stenosis but not in their postoperative state. In septal defects, the Vectorcardiogram correlates poorly with the shunt size but well with the pulmonary and right ventricular pressures. It is of interest that the counter clockwise superior plane loop of the endocardial cushion defect could be separate from that found in atrial secundum and ventricular septal defects by the timing of the superior portion of the loop. However, this did not hold true in pulmonic stenosis and other defects.

Dr. Ellison, who now holds the position of Associate Professor at Georgetown University Medical Center and Dr. Restieaux, have done an excellent job of demonstrating the value of Vectorcardiography in congenital heart disease. The text, although at times difficult to read because of the technical nature of the material, does not suffer from the ponderous language of some Vectorcardiographic literature. Most of the diagrams and illustrations are excellent. I believe the book could benefit from the expansion of normal Vectorcardiograms, particularly those depicting the first 24 and 48 hours of life.

This is not a book to be casually read but one that must be studied thoroughly. Although its major value will undoubtedly accrue to those few who perform Vectorcardiography on infants and children and those who specialize in Pediatric Cardiology, this book may be of value also to those Cardiologists who are at times required to evaluate electrocardiograms of children with proven or suspected congenital heart disease. A copy should reside in their library or their hospital's library.

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Actions. Antiminth (pyrantel pamoate) has demonstrated anthelmintic activity against *Enterobius vermicularis* (pinworm) and *Ascaris lumbricoides* (roundworm). The anthelmintic action is probably due to the neuromuscular blocking property of the drug.

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Indications. For the treatment of ascariasis (roundworm infection) and enterobiasis (pinworm infection).

Warnings. *Usage in Pregnancy:* Reproduction studies have been performed in animals and there was no evidence of propensity for harm to the fetus. The relevance to the human is not known.

There is no experience in pregnant women who have received this drug.

Precautions. Minor transient elevations of SGOT have occurred in a small percentage of patients. Therefore, this drug should be used with caution in patients with pre-existing liver dysfunction.

Adverse Reactions. The most frequently encountered adverse reactions are related to the gastrointestinal system.

Gastrointestinal and hepatic reactions: anorexia, nausea, vomiting, gastralgia, abdominal cramps, diarrhea and tenesmus, transient elevation of SGOT.

CNS reactions: headache, dizziness, drowsiness, and insomnia. Skin reactions: rashes.

Dosage and Administration. *Children and Adults:* Antiminth Oral Suspension (50 mg. of pyrantel base/ml.) should be administered in a single dose of 11 mg. of pyrantel base per kg. of body weight (or 5 mg./lb.); maximum total dose 1 gram. This corresponds to a simplified dosage regimen of 1 cc. of Antiminth per 10 lb. of body weight. (One teaspoonful = 5 cc.)

Antiminth (pyrantel pamoate) Oral Suspension may be administered without regard to ingestion of food or time of day; and purging is not necessary prior to, during, or after therapy. It may be taken with milk or fruit juices. Because of limited data on repeated doses, no recommendations can be made.

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*Data on file at Roerig.
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The Language of Fractures. ROBERT J. SCHULTZ, M.D. Price, $22.50. Pp. 394 with illustrations. Baltimore: The Williams & Wilkins Company, 1972.

This book represents the best introduction to fractures that I have seen. It presents a foundation of fracture vocabulary in general, and then proceeds to the application of the general descriptions to specific regions. Fundamentals of pertinent anatomy are given along with descriptions of mechanisms of injuries that produce the various specific fractures. The text is succinct, lucid and well supported by excellent anatomic drawings and X-ray reproductions illustrating virtually all common fractures.

The book is not intended as a guide to treatment, rather it is an introduction and guide to the diagnosis and description of fractures.

There is a section on fracture eponyms and a chapter on the anatomic variants that are often misread as fractures on radiographs. Both of these sections are well done and will be welcomed by the novice or non-orthopaedist who is often confronted with a bewildering array of eponyms and/or the decision as to whether a given fragment on an X-ray represents an anatomic variant or a fracture.

The appeal of this book is quite wide. For students and non-orthopaedists it will be useful as an introduction to fractures. In addition, it fills a void in the orthopaedic literature for the beginning orthopaedic resident in its concise, yet authoritative introduction to the musculoskeletal trauma that he will be dealing with for the remainder of his career. Finally, for the orthopaedic surgeon, the book is an interesting and useful review, particularly with reference to the sections on eponyms and radiographic anatomical variants. The bibliography is very valuable in that it provides quite a complete set of references for the original descriptions of most fractures.

I feel that this book should be required reading for all beginning orthopaedic residents and should be at least available to any other members of the profession who are concerned with the evaluation of patients who have sustained musculoskeletal trauma.

STEPHEN S. HAAS, M.D.

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Common Problems in Office Practice. ROBERT B. TAYLOR, M.D. Price, $9.95. Pp. 402. Hagerstown, Maryland: Harper & Row, 1972.

It is difficult to find an appropriate place for Dr. Taylor's book, as it provides relatively little information about a great many illnesses. The list of diseases, however, is incomplete, just as is the description and treatment prescribed for most of the entities.

Dr. Taylor begins with a fairly common sense approach to management of an office practice, making some useful suggestions such as the need to "hire enough help" and to limit one's patients to a number and a geographic area such that complete care, including house calls, can be given.

He then proceeds to review the various categories of illness that he has encountered in 12 years of family practice in upstate New York.

The section on Internal Medicine, of which I am perhaps too critical because it deals with my specialty, tends to be simplistic, incomplete, and occasionally inaccurate. There is not enough detail to really tell one how to manage a case.

On the other hand, the Dermatology, Urology, Surgery and Orthopedic sections have some good ideas on patient handling, as when dealing with acne and enuresis. They are spotty, however, and leave certain diseases frequently encountered, such as non-specific urethritis and De Quervain's disease, out entirely. Pediatrics deals largely with well baby care, but does not discuss growth and development at all.

The bibliographies are short, contain a fair number of standard textbook references and usually one or two recent articles on the subject matter, perhaps more than its share from Post Graduate Medicine.

Thus, Dr. Taylor's book turns out to be a listing of the diseases he has encountered in family practice with some useful patient handling information about an occasional illness, but no authoritative account of disease or its treatment that can serve as a guide to the practitioner. There are briefer, more accurate, and more complete accounts of the management of all the diseases Dr. Taylor mentions in such readily available texts as Conn's "Current Therapy," and Ferguson's "Surgery of the Ambulatory Patient." Dr. Taylor's book, lacking illustrations, is severely limited in its description of surgical techniques.

It is possible that certain paramedical personnel such as nurses and aides might gain some insight into the handling of common office problems from Dr. Taylor's book, but I think it offers the family physician little help.

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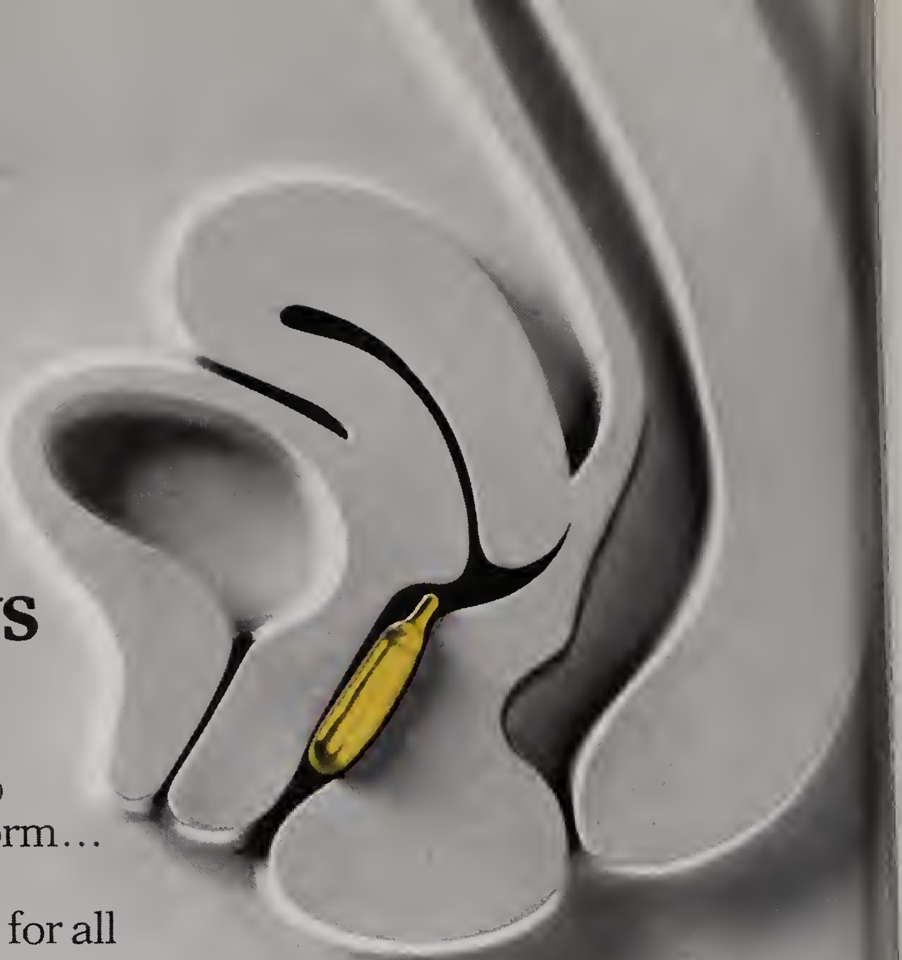

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Supportive Care of the Surgical Patient. WILLIAM M. STAHL, M.D. Price, $13.50. Pp. 270. New York: Grune & Stratton, 1972.

The author presents the subject matter in a slightly different manner and at times has a philosophical approach, as compared with the usual presentation of a surgical treatise, with emphasis on ecological and environmental considerations. His evaluation of the patient stresses physiological disturbances which take place resulting from environmental exchange, internal transport and emotional mechanisms. There is basic physiological data as is found normally to maintain the body in the healthy state, changes which take place following traumatic injury and/or surgery, disease and infection along with emotional factors, all of which play an important role in the response to the survival systems.

These exchange systems are discussed separately to include as Part I—Respiratory System, Alimentary Tract, Kidney and Skin. Part II comprises the Transport Systems—Cardiovascular and Body Fluids. Part III deals with the Liver, Endocrine, Autonomic Nervous System and emotional factors.

Under each heading the primary function and physiology, anatomy requirements during pre-, intra and postoperative care and complications are considered. References supporting the text are to be found readily at the end of each separate subject previously mentioned i.e. Respiratory System 1-1 to 1-67; Alimentary Tract 2-1 to 2-110; similarly, the Kidney, Skin and Cardiovascular Systems are annotated. Authors of the references appear chiefly to be physiologists and those in research although the names of clinical surgeons are easily recognized.

Examples of the author's style follow: Exchange System (Kidney) Postoperative Care: "Maintenance of the normal ventilation and perfusion state is equally important in the postoperative period if renal function is to be preserved. Patients with low preoperative clearance measurements should have interval-clearance measurements performed in the postoperative period. In any patient after serious surgery or trauma, especially involving hypovalemia, tissue damage, and/or transfusion, a decrease in renal function may occur . . ." Transport System (Cardiovascular System) Postoperative Care: "Careful attention of the clinical state of the patient and proper use of monitoring, both electrical and chemical, is essential. Cardiac rate and rhythm, blood pressure, skin color and turgor, central venous pressure, urine output, chest auscultation, blood gases and mental state remain the important parameters."

This book is extremely interesting and can be well recommended since it gives an erudite viewpoint on this important aspect of patient care.

JOHN STUBENBORD, M.D.

Hereditary Retinal and Choroidal Diseases. ALEX E. KRILL, M.D. Price, $19.75. Pp. 354 with illustrations. Hagerstown, Maryland: Harper & Row, 1972.

In Volume I, the author has attempted to provide us with "tools" to build upon our knowledge of hereditary diseases of the retina and choroid. He has done so by discussing those disciplines, techniques, and modalities that are currently available to evaluate those conditions. His first chapter on principles of genetics is a necessary first step to understanding the hereditary disorders. However, from the standpoint of the general ophthalmologist I believe that it is too detailed. The second chapter dealing with fluorescein is superb. It should be read not only by those ophthalmologists sub-specializing in diseases and surgery of the retina but also by those who are referring patients to have these studies performed. The chapters dealing with night vision, the ERG, the EOG, and visually evoked responses (VER) are useful not only for reviewing the techniques involved but also for demonstrating their diagnostic usefulness in specific hereditary disease entities of the retina and choroid. The chapter on color vision evaluation will be helpful to the resident in training as well as to the practicing ophthalmologist who desires a quick review of the subject. I would recommend the addition of this text to the library of all ophthalmologists. It is tragic that such a gifted author will be unable to continue his brilliant career due to his untimely death in a recent air tragedy.

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Prepared By
The Department of Radiology
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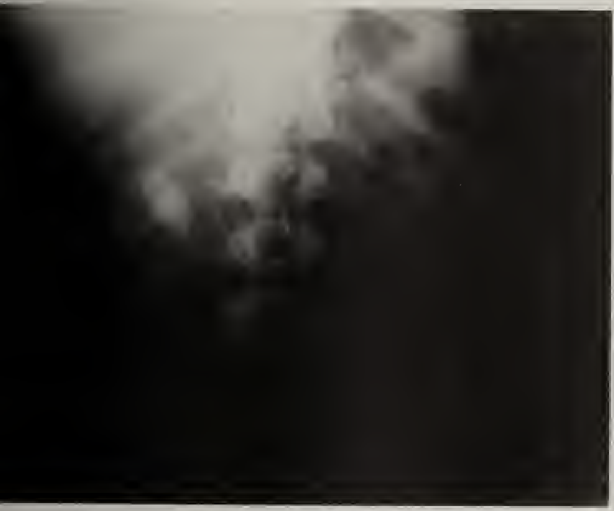
A 30 year old male with long-standing history or urinary tract infection with calculi. He was admitted for work-up which included Excretory Urograms and Angiogram.



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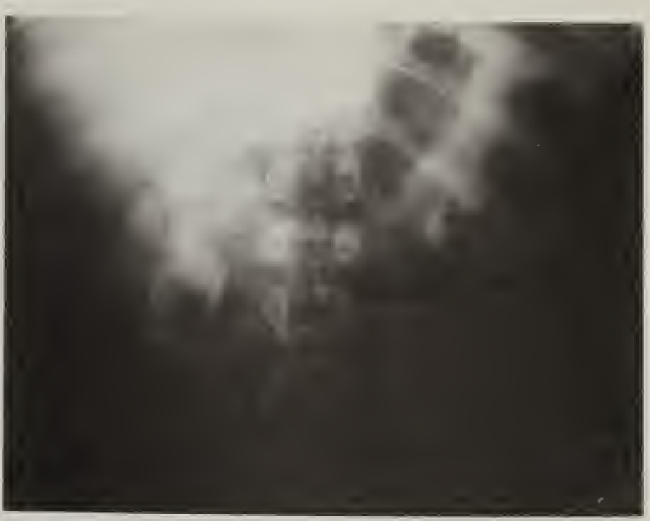
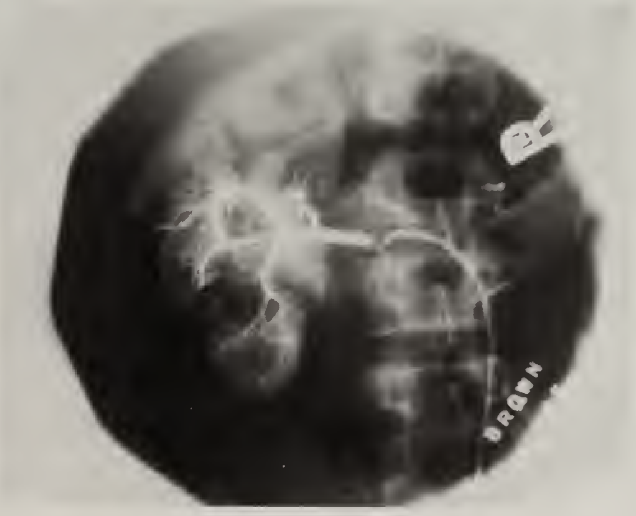


EXCRETORY UROGRAM



SELECTIVE ANGIOGRAM

XANTHOGRANULOMATOUS PYELONEPHRITIS

DIAGNOSIS:

The Excretory Urogram shows a staghorn calculus on the right filling most of the renal pelvis and proximal ureter. There are several smaller stones lateral to this. The drainage structures are dilated and the renal cortex in several areas is markedly thinned. A mass is present in the lower pole, projecting from the lateral margin of the kidney. The left kidney shows similar, though less marked, changes in the superior pole.

An Arteriogram (selective injection into the lower of renal arteries) demonstrates stretching of intra-renal branches and neovascularity superior-medially.

Xanthogranulomatous Pyelonephritis is a chronic suppurative pyelonephritis, often with stones and obstruction. The process can diffuse or present as a sizable mass lesion. There is no single causative agent and there are a multitude of bacterial findings. Histologically, foam cells are present which resemble somewhat the large clear cells seen in renal cell carcinoma.

Arteriographically, the tumefaction type of xanthogranulomatous pyelonephritis is often avascular but can have a bizarre neovacularity like a renal cell carcinoma.

Surgery was performed to remove the stones and drain a multilocular abscess.

Edited by Gunter J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

Charles K. Holmes, M.D.
1891–1973

Dr. Charles K. Holmes, Washington-area physician and surgeon, died on April 5, 1973. He resided at 6205 Kennedy Drive, N.W., Washington, D.C.

Born in St. Paul, Minn., he received a Ph.B. degree from Hamline University in St. Paul, and his M.D. degree from the University of Minnesota, Minneapolis, Minn. He served his internship at the Bismarck Clinic in Bismarck, North Dakota and three separate residencies in the U.S. Army (1917-1919, 1941-1946, and 1948-1952). His early positions with the army included the post of Commanding Officer, Med Tech School, Army & Navy Hospital, Hot Springs, Arkansas, and service with the U.S. Control Group, London, Public Health Occupation of Germany. During his later years with the armed services, Dr. Holmes was with the Office of the Surgeon General as Colonel, MC, Executive, Civilian Component Activities. He also served on the staffs of Asbury Hospital, Minneapolis, and St. Mary's Hospital, Minneapolis; as Assistant Instructor of the University of Minnesota's Outpatient Clinic; and as the sole medical consultant for the National Association of Letter Carriers Health Benefit Plan in Washington.

Dr. Holmes was a member of the American Medical Association, the Hennepin City Medical Society and an Associate Member of the Medical Society of the District of Columbia for 24 years.

He is survived by his wife Mabel Jane, of the home; his son, Charles K. Holmes, Jr., of Atlanta, Ga., his brother, Dr. Frank O. Holmes of Boston, Mass., and three grandchildren.

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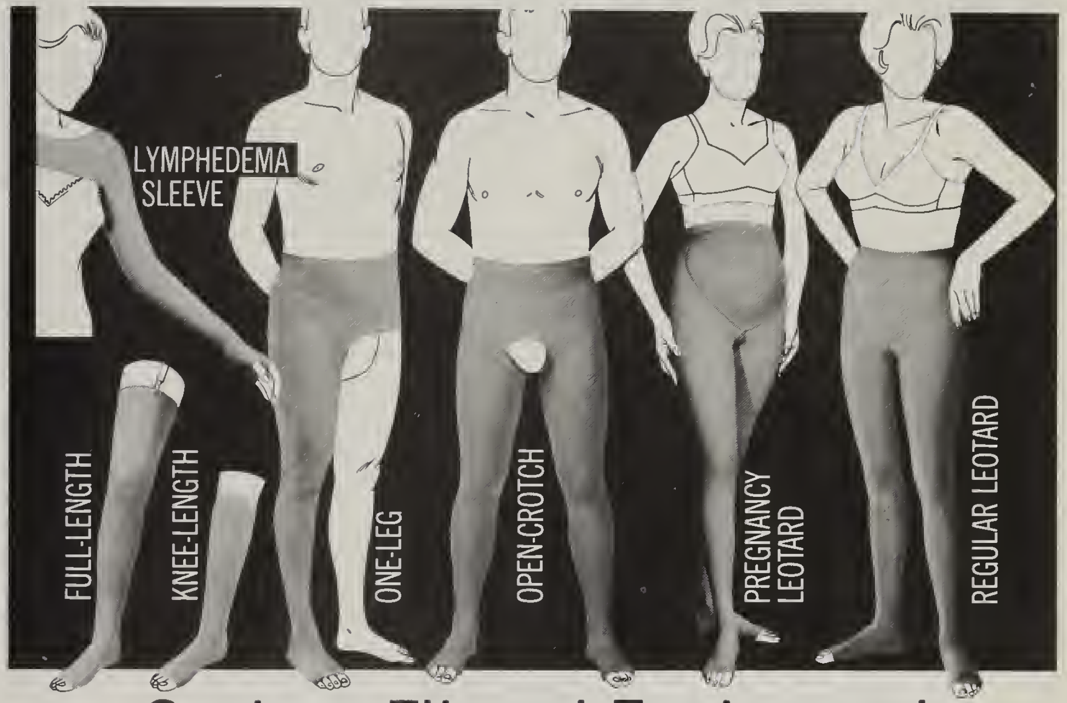
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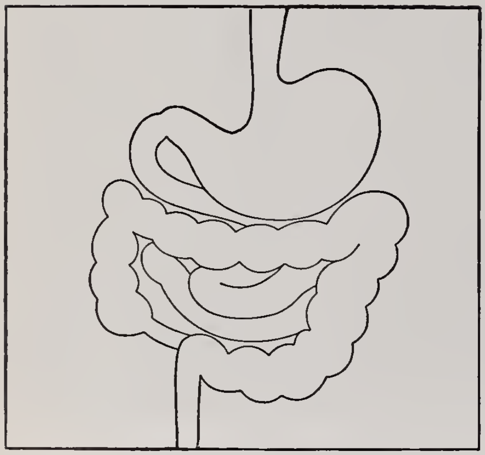
in "Gasspastic" conditions



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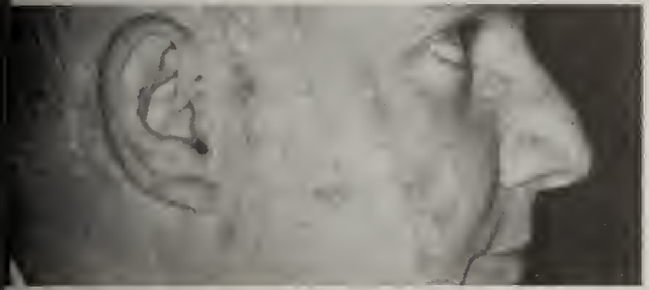

atient P.T. seen on 3/29/67 shows typical lesions of noderately severe keratoses. Note residual scarring on idge of nose from previous cryosurgical and electro- urgical procedures.*

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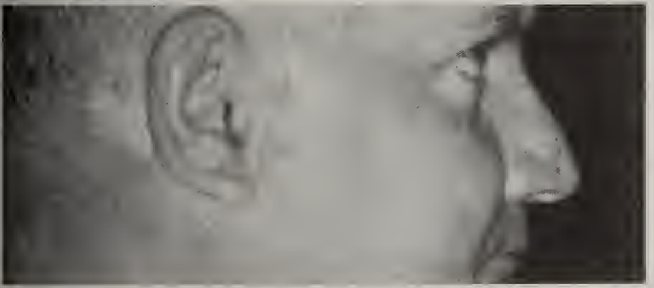

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index of advertisers

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- Jobst Institute Service Centers 9

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- Mutual of Omaha C3
- Ralph W. Lee & Co. T-309
- Russell, Marsh & Kennedy 11

Investment Planning

- Suter Associates Retirement Planning Company 17
- U. S. Tree Farms System, Inc. T-298

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- Association of Undergraduate and Practical Nurse Registry T-304
- District of Columbia Manpower Administration T-310

Nutrition Education

- Dairy Council of Greater Metropolitan Washington, D.C. T-308

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- Burton, Parsons & Company, Inc. T-316
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- Julius Schmid, Inc. T-312–313
- G. D. Searle & Company T-300–302
- The Upjohn Company 5

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- Peoples Drug Stores T-296

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- Anderson Stokes 13
- Shannon & Luchs T-310

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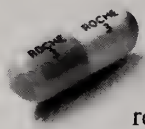

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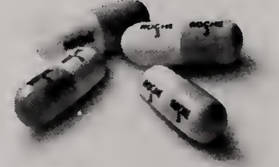

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President's Message 1

Editorials 3

SCIENTIFIC ARTICLES

Acute Pancreatitis with Extensive Peripheral Fat Necrosis Simulating Erythema Nodosum and an Abdominal Cyst. William O. Dobbins III, M.D. and Martin S. Liberman, M.D. 319

Estimation of the Number of Narcotic Addicts in an Urban Area. Robert L. DuPont, M.D. and Thomas E. Piemme, M.D. 323

Hypercalcemia During the Diuretic Phase of Acute Renal Failure. Robert Wilson, M.D., Carlos Raposo, M.D., Ranganathan Venkatesan, M.D., Royce Lin, M.D., Anne Thompson, M.D., Atin Guha, M.D., Norman Kramer, M.D. and Alvin E. Parrish, M.D. 327

Hepatitis Virus B Infection in an Alcoholic with Cirrhosis. Howard Heit, M.D. and William O. Dobbins, III, M.D. 331

Severe Multisystem Allergic Reaction to Sulfisoxazole. Howard Goldsweig, M.D., Carl Whipplinger, M.D., Geraldine Schechter, M.D. and Lawrence Lessin, M.D. 334

The Influence of Medical School on Selection of Career Specialties. Stephen A. Schroeder, M.D. and Alan Schliftman 339

SPECIAL ARTICLES

From the Editors 345

Information to Authors 347

OTHER FEATURES

ECG Problems 322

The View Box 350

New Members 355

Obituaries 365

(continued)

Book Reviews 367
Pathogenic Mycoplasmas. (Ciba Foundation Symposium) Reviewed by Thomas McPherson Brown, M.D.

Clinical Nephrology. (Papper) Reviewed by Alvin E. Parrish, M.D.

Cardiac Hypertrophy. (Alpert) Reviewed by Benjamin Manchester, M.D., F.A.C.P.

Classified Advertising 13

Index to Advertisers 14

Advertising and Subscription Information 14

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Irving Burka, M.D.

Midsummer Daydreaming

In these warm lazy days of summer, when activity is at its slowest, I have had reveries of how nice it would be IF

–there were no computers to depersonalize us into account numbers;
–there were no mounds of forms to fill out;
–there were no Phase III;
–all the ills of the country would not be blamed on Medicine;
–there were no gasoline shortage;
–the dollar was as strong as it once was;
–there weren't so many lay busybodies who have suddenly become experts on the Practice of Medicine;
–I were once again a physician, rather than a "provider";
–medical students were to learn and take interest in the economics of medicine;
–we Americans were not so "litigation happy";
–Arabs would live at peace with the Israelis;
–racial bias disappeared;
–television media would give us equal time to reply to allegations against us;
–the hotels provided sufficient parking for those attending functions;
–the President's Commission on Malpractice would not have muddied the waters;
–there were adequate extended facilities for the elderly at reasonable charges;
–there were no Monday mornings;
–it didn't rain on my day off;
–just once Marcus Welby did not have all the answers:

Summer is such a pleasant time for dreaming–an interlude between the harshness of winter and the briskness of autumn. Hope you are having a nice summer.

Irving Burka

Just what do you get for your AMA dues?

You get a package of personal and professional services and benefits you've probably never been fully aware of.

You get insurance programs at a cost considerably lower than those purchased on an individual basis. A $250,000 Excess Major Medical Policy. Group Life. Disability Income Insurance. Professional Liability Insurance (in co-sponsorship with your state society.) Then there's the AMA Members Retirement Fund.

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American Medical Association
535 N. Dearborn St./Chicago, Ill. 60610

THE IRRELEVANCE TO TRUTH OF MAJORITY OPINION AND AUTHORITY

A Perspective on Peer Review Systems

Experience is fallacious and judgement difficult.
Hippocrates

"What is truth?" This profound and unanswered question was asked by the Roman governor, Pontius Pilate, in a philosophical moment when Jesus of Nazareth was arraigned before him. He used the question as the only way out of his judicial dilemma. He had to choose whether to base his decision on justice or on political expediency. The accounts in the four Gospels make clear that Pilate was convinced of the innocence of the defendant, but was moved by political considerations to permit the death sentence.

Jesus was charged with "perverting the people,"[1] which would have been a Roman federal crime, and with claiming to be a king, which would be treason if it could be sustained that "whosoever maketh himself a king, speaketh against Caesar."[2] It is clear that on the merits, Pilate dismissed both charges.[3] He perceived that envy was the motivation on the part of the entrenched Establishment[4] and that many bore false witness.[5] He also saw that a riot might result if he did not allow the execution, so that "to content the people,"[6] he delivered Jesus to be crucified after publicly washing his hands of "the blood of this just person," in a symbolic ceremony.[7]

But apparently Pilate had to justify in his own mind this placement of political expediency above justice. It was from his own interrogation of Jesus that he found his escape. "Art thou a king then?" Jesus replied, "Thou sayest that I am a king. To this end was I born, and for this cause came I into the world, that I should bear witness unto the truth. Every one that is of the truth, heareth my voice." Here Pilate made his poignant comment, "What is truth?"[8]

But if truth, like other profundities, eludes absolute definition, faith in the concept has been one of the most tenacious of human guiding principles. "And ye shall know the truth, and the truth shall make you free."[9]

How best to get at the truth has been the perennial problem. In our society the attempt has been made to offset the bias of the prejudices which all men have, with a system of jurisprudence which decrees that everyone is entitled to trial by a jury of his peers. But the perception is widespread that peers may themselves be so biased that justice is better obtained through trial by a judge. Hence, many defendants elect the latter in preference to a jury.

It is beyond challenge that the bench presumes the highest qualification and preparation on the part of its incumbents, although this is certainly not always the case. The business of passing official judgments, however, requires full time and is not something to be foisted upon a whole profession as an added responsibility.

It would be premature at this stage of experience to define peer review, what it encompasses, what it excludes and how it would interdigitate with the substantial body of extant law governing professional standards and practices. Furthermore, both dissents and challenges arising out of peer reviews from both within and without the profession would have to be tried in the courts before the scope and limitations of such a system could be determined.

As physicians would perforce become more legal minded there would be increasing attention to the weight of majority opinion and of authority. Gradually these two might become merged in the same fountainhead. To ensure that the best interests of the people are served by the medical profession, it is presently pertinent to point out that neither majority opinion nor authority has any relation to truth.

In 1492 the majority of people believed the earth was flat and Columbus was in a definite minority in holding that it was round. Yet the minority was proved right and the majority wrong. Today ask any group of people to lay a hand, palm down, on a table and identify for them the prominence of the head of the ulna. Then ask them if they are looking at the front or at the back of the head of the ulna. The majority, educated or not, medical or lay, will say it is the back because it appears to be on the back of the forearm. However, it is the front, because in the movement of pronation to place the palm downward, only the radius moves. "Skim milk masquerades as cream, things aren't always what they seem."

As to authority, let us take the case of Copernicus, the 500th anniversary of whose birth the world celebrates this year. In 1543 the revolutionary theory, known by his name, that the sun was the center of the solar system about which the planets revolve, was published as he lay on his death bed. This upset the geocentric concept of the established Ptolemaic astronomy and invited the attention of the Inquisition, but Copernicus was beyond reach.

When Galileo, the most famous scientist of his period, however, demonstrated in 1613 that Copernicus was right and Ptolemy wrong, the opposition consolidated against him. He was secretly denounced to the Inquisition for blasphemous utterances which had been freely invented. By official decree of the church in 1616, Copernicanism was declared false and erroneous and the teaching of the heretical doctrine of the rotation of the planets around the sun and the diurnal rotation of the earth on its own axis was strictly forbidden. In 1632 Galileo produced a great work, "Dialogue of the Two Chief World Systems," with the approval of the censors, which was acclaimed a masterpiece throughout Europe, but the critics denounced it as a plea for the Copernican system. He was brought to trial by the Inquisition in 1633, convicted of having "held and taught" the Copernican doctrine, ordered to recant and condemned to house arrest for the remainder of his life. This was the ultimate in assertion of the weight of authority, yet our satellites now freely orbit the earth, visit the moon and are beginning the exploration of the neighboring planets of Venus, Mars and Jupiter.

One is reminded of the comment of Lear in his madness to Gloster, "Thou hast seen a farmer's dog bark at a beggar?" "Ay, sir." "And the creature run from the cur? There thou might'st behold the great image of authority; a dog's obeyed in office."

The Hippocratic aphorism that "experience is fallacious and judgement difficult," expresses a common recognition on the part of physicians that neither majority opinion nor authority should be controlling in determining what is best for a patient. When the gravity of a patient's condition requires the evaluations of four or five consultants, the decision on treatment is not made by taking a vote or throwing the weight of authority. It is made in humility by honest experts pooling their knowledge for the benefit of a case which is intrinsically unique, with full knowledge they could all be wrong. The medical profession as a class is thus accustomed to sitting in judgement, is keenly aware of its probable error and is, therefore, properly modest.

Peer review, however, involves another kind of sitting in judgement which requires the most careful scrutiny as to all its implications and *modi operandi* before general adoption. Already misgivings and apprehension have been expressed in some areas as to how the reviewing bodies shall be constituted and how equitable administration is to be assured.

While the nebulous aspects of the situation are being clarified, and without misoneism, it would be well for physicians to remember that mechanisms for dealing with professional misconduct already exist and to remember also the admonotions in the Sermon on the Mount:

> Judge not, that ye be not judged. For with what judgment ye judge, ye shall be judged; and with what measure ye mete, it shall be measured to you again. And why beholdest thou the mote that is in thy brother's eye, but considerest not the beam that is in thine own eye? Or how wilt thou say to thy brother, Let me pull out the mote out of thine eye; and, behold, a beam is in thine own eye? Thou hypocrite, first cast out the beam out of thine own eye; and then shalt thou see clearly to cast out the mote out of thy brother's eye.

W. MONTAGUE COBB, M.D.

References

1. Luke, 23:14
2. John, 19:12
3. Matt., 27:23-24; Mark, 15:14; Luke, 23:14-16, 22; John, 18:38; 19:6
4. Matt., 27:18; Mark, 15:10
5. Mark, 14:55-59
6. Mark, 15:15
7. Matt., 27:24
8. John, 18:37-38
9. John, 8:32

A Conceptual Model for Rehabilitation

Dorland[1] defines Rehabilitation as "the restoration to useful activity of individuals who have been wounded so as to suffer physical or emotional disability, such restoration including treatment and training to fit the individual for occupation in industry." Traditionally, the rehabilitation process was applied to the care and treatment of patients with overt physical impairments. Its application or role in the whole of medicine was poorly defined. Even in 1973, rehabilitation is often considered a process separate from, rather than a part of, usual medical or surgical practice.

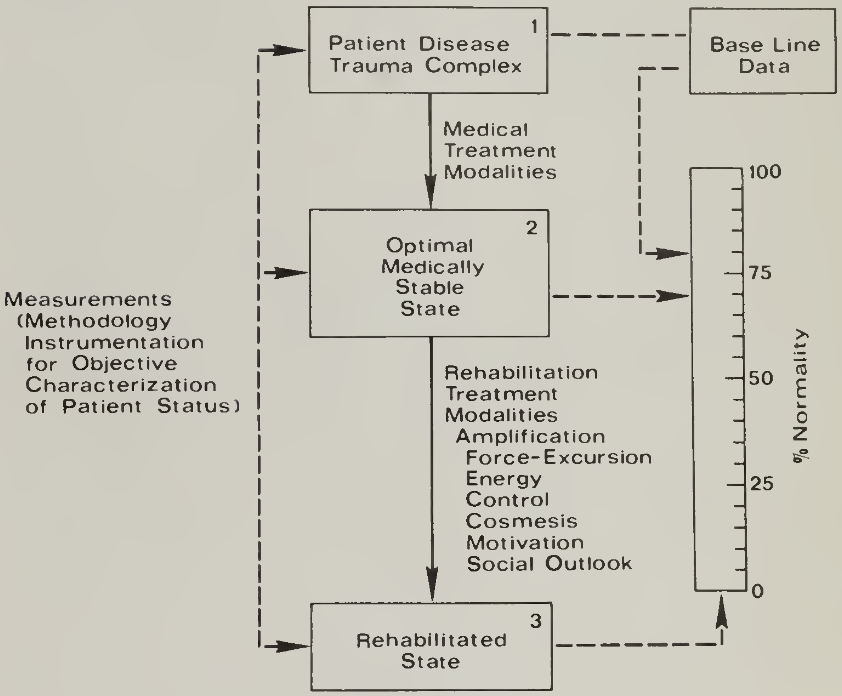
In a period of ever increasing numbers of patients with chronic diseases, which are often complicated by physical and/or emotional disability, physicians must re-evaluate their roles and responsibilities in the rehabilitation process. If, in Dorland's definition, *diseased* is substituted for *wounded*, it would be apparent that every physician practices at least some of the principles of rehabilitation. In other words, rehabilitation is directed to providing treatment for a patient from the onset of illness until that patient has achieved an optimal physiological, psychological, vocational and sociological adjustment. These adjustments may be at the patient's original level prior to illness or at lower or higher levels, depending on his adaptive capacity. The rehabilitation process also includes the maintenance of these optimal levels, once achieved, as well as the application of those methods which prevent or delay further advancement of the underlying disease process[2].

Thus, it is within the province of rehabilitation:

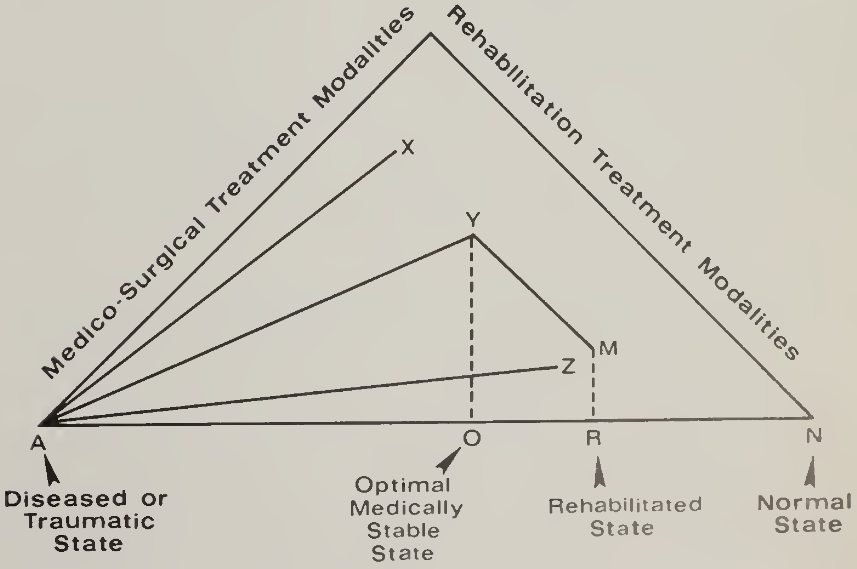
1. to develop appropriate methodologies, instrumentations and techniques to diagnose and measure specific impairments;
2. to develop appropriate treatment to achieve as optimal a recovery as possible; and
3. to enhance or amplify a patient's potentials by providing those aides which allow him to become competitive in daily living and vocational activities.

This process is diagrammed in Figure 1. The main flow of the diagram is from 1 to 3. The rehabilitation process begins with the recognition that a patient has an impairment. Inherent in the application of the process is adequate diagnosis and implementation of proper treatment for the disease or its associated complications. When a patient attains an optimal medical stable state, as a result of treatment, his physiologic, psychologic, vocational and sociologic characteristics are measured. Thereafter, added interventions are prescribed and implemented as warranted. The treatments will vary with the disease process and can include single or multiple interventions. These efforts result in the elevation of a patient to the rehabilitated state. Inherent throughout the process is repeated periodic evaluation by measurements and comparison with baseline data. For many patients, achievement of the rehabilitated state will terminate the need for further therapy (burn patients with satisfactory plastic repair and healing) while for others continued maintenance and application of preventive techniques are imperative, such as in patients with coronary heart disease, stroke, obstructive pulmonary disease and alcoholism.

REHABILITATION SCHEMATA


1
Patient Disease Trauma Complex
Base Line Data
Medical Treatment Modalities
2
Optimal Medically Stable State
Measurements (Methodology Instrumentation for Objective Characterization of Patient Status)
Rehabilitation Treatment Modalities
Amplification
Force-Excursion
Energy
Control
Cosmesis
Motivation
Social Outlook
3
Rehabilitated State
100
75
50
25
0
% Normality

HEURISTIC PLOT OF REHABILITATION PROGRESS


Medico-Surgical Treatment Modalities
Rehabilitation Treatment Modalities
X
Y
M
Z
A
O
R
N
Diseased or Traumatic State
Optimal Medically Stable State
Rehabilitated State
Normal State

In Figure 2, we represent a heuristic device for plotting progress from the diseased to the normal state as a result of medical, surgical and rehabilitation treatment. Lines such as AX, AY and AZ represent relationships between treatment and progress from the diseased to the normal state. Movement from left to right, along the base of the triangle, is a function of the disease and treatment modality; that is, lines AX, AY and AZ have varying slopes. Surgical treatment, such as amputation of a limb necessitated by compromised blood supply, may result in a medically stable state that is further from the normal state than a state obtained by treatment of a myocardial infarct. In the former, the line AX may represent the treatment-progress interaction, whereas in the latter line AZ may delineate the process. Progress from the optimal medically stable state represented by Y to the rehabilitated state, point M, is achieved through rehabilitation treatment, as, for example, along line YM. Thus, point M is reached as a result of both types of treatment, medico-surgical and rehabilitative. These modalities are, in accordance with our thesis, mutually dependent, and are so represented on the triangular plot.

Perhaps the most difficult aspect of the rehabilitation process is the need for an interdisciplinary team approach. The composition and characteristics of a team will vary with each clinical problem. For instance, for a patient with peripheral vascular disease, a rehabilitation team may include an internist or peripheral vascular specialist, orthopedist, orthotist, clinical engineer, and physical therapist; while the team for a cardiac patient may be composed of a cardiologist, nutritionist, social worker, psychiatrist and/or clinical psychologist and physical educator. It is to be noted that while each member of the team contributes his expertise to the overall process of rehabilitation, the physician that has primary responsibility for the patient's well being assumes the role of team leader.

JOHN NAUGHTON, M.D.
Director of Rehabilitation Medicine
FRED LEONARD, Ph.D.
Research Professor of
Medicine and Orthopedics

References

1. Dorland, The American Illustrated Dictionary, 22nd Edition, Saunders.
2. Naughton, J., Bruhn, J., Lategola, M. T., and Whitsett, T. Rehabilitation Following Myocardial Infarction. Am. J. Med. 46: 725-734, 1969.

The diabetic who has too much...
too much sugar, too much fat.

Maybe the last thing she needs is more of her own insulin. Especially when you consider that many overweight diabetics already have normal or high levels of endogenous insulin and that insulin is lipogenic.

If she just won't diet and oral therapy is indicated in adult-onset, nonketotic diabetes...

DBI-TD® Geigy
phenformin HCl

lowers blood sugar without raising blood insulin.

For complete details, including dosage, please read the prescribing information. It's summarized below.

DBI® phenformin HCl
Tablets of 25 mg.
DBI-TD® phenformin HCl
Timed-Disintegration
Capsules of 50 and 100 mg.

Indications: Stable adult diabetes mellitus; sulfonylurea failures, primary and secondary; adjunct to insulin therapy of unstable diabetes mellitus.
Contraindications: Diabetes mellitus that can be regulated by diet alone; juvenile diabetes mellitus that is uncomplicated and well regulated on insulin; acute complications of diabetes mellitus (metabolic acidosis, coma, infection, gangrene); during or immediately after surgery where insulin is indispensable; severe hepatic disease; renal disease with uremia; cardiovascular collapse (shock); after disease states associated with hypoxemia.
Warnings: Use during pregnancy is to be avoided.
Precautions: 1. *Starvation Ketosis:* This must be differentiated from "insulin lack" ketosis and is characterized by ketonuria which, in spite of relatively normal blood and urine sugar, may result from excessive phenformin therapy, excessive insulin reduction, or insufficient carbohydrate intake. Adjust insulin dosage, lower phenformin dosage, or supply carbohydrates to alleviate this state. **Do not give insulin without first checking blood and urine sugar.**
2. *Lactic Acidosis:* This drug is not recommended in the presence of azotemia or in any clinical situation that predisposes to sustained hypotension that could lead to lactic acidosis. To differentiate lactic acidosis from ketoacidosis, periodic determinations of ketones in the blood and urine should be made in diabetics previously stabilized on phenformin, or phenformin and insulin, who have become unstable. If electrolyte imbalance is suspected, periodic determinations should also be made of electrolytes, pH, and the lactate-pyruvate ratio. The drug should be withdrawn and insulin, when required, and other corrective measures instituted immediately upon the appearance of any metabolic acidosis.
3. *Hypoglycemia:* Although hypoglycemic reactions are rare when phenformin is used alone, every precaution should be observed during the dosage adjustment period particularly when insulin or a sulfonylurea has been given in combination with phenformin.
Adverse Reactions: Principally gastrointestinal, unpleasant metallic taste, continuing to anorexia nausea and, less frequently, vomiting and diarrhea. Reduce dosage at first sign of these symptoms. In case of vomiting, the drug should be absolutely withdrawn. Although rare, urticaria has been reported, as have gastrointestinal symptoms such as anorexia, nausea and vomiting following excessive alcohol intake (B) 98-140-103-E (6/72)

For complete details, including dosage, please see full prescribing information.

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What should a medication for sleep be expected to provide?

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychologica dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with

Sleep for 7 to 8 hours without need to repeat dosage during the night

No sleep medication has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia patients given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer nighttime awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to repeat dosage during the night.

Sleep with consistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration. Thus there is little likelihood for the need to increase dosage to maintain therapeutic effect.

Dalmane (flurazepam HCl) is a distinctive sleep medication—a benzodiazepine specifically indicated for insomnia. It is not a barbiturate or methaqualone, nor is it related chemically to any other available hypnotic.

Sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dalmane; no depression of cardiac or respiratory function was noted in patients administered recommended or higher doses for as long as 90 consecutive nights. Dalmane is generally well tolerated and morning "hang-over" is relatively infrequent. Dizziness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in elderly and debilitated patients. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

DALMANE®
(flurazepam HCl)
When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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t depression or suicidal tendencies. dic blood counts and liver and kid- unction tests are advised during ated therapy. Observe usual precau- in presence of impaired renal or tic function.

rse Reactions: Dizziness, drowsi- lightheadedness, staggering, ataxia alling have occurred, particularly lerly or debilitated patients. Severe tion, lethargy, disorientation and , probably indicative of drug intoler- or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, [illegible] and elevated SGOT, SGPT, [illegible] bilirubins and alkaline [illegible] Paradoxical reactions [illegible] excitement, stimulation and hyperactivity [illegible] also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. Adults: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 [illegible] 30 mg flurazepam HCl.

Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American
Pharmaceutical
Association

"Too many doctors are indiff ent to the economic consequence their decisions." So stated a recen issue of *Medical News Report* (December 4, 1972), an independent weekly newsletter published by for AMA Chief Executive F. J. L. Blasingame, M.D.

Doctor, are you indifferent . . . ?

In discussing an anticipated i crease in Blue Shield rates, Dr. Bla ingame's newsletter had this to say

"In general, it can be said, MD have given the impression they are not particularly concerned with the increase in cost of health care to th patients . . .

"True, an MD's training is primarily scientific, but in the real wo of practice, all of his scientific decisions have a price tag, or an econo impact. The economics of health ca beckon the practitioner's attention Concern for economics of medicine

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical
Manufacturers
Association

When the pharmacist recommends that a drug product other th the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is nece sary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, the unilateral decision of the pharmacis made in the absence of clinical know edge of the patient, could expose him to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothin in the pro-substitution argument that offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowledge about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degree puts him at a disadvantage. Most often, a practicing physician will need expert knowledge of no more than 25

Advertisement

uld be an obligation of medical
ictice…
"Medical societies ought to con-
ct continuing campaigns to point
the substantial savings that could
realized thru deductible insurance
d protection for catastrophic ill-
ss. At the very least, they should, in
patients' interest, question the
tics of any insurance organization
it raises health care costs by forc-
policyholders to buy insurance
y may not need or want and prob-
y won't ever use.
"Too many doctors are indiffer-
t to the economic consequences of
ir decisions. Too many, for ex-
iple, habitually hospitalize patients
the convenience of the MD. It's
nsense to deny such habits exist…
"Doctors, thru their medical so-
ties, have unhesitatingly appealed
their patients for support in the
ht against government interference
h the private practice of medicine.
d the public in the past has re-
onded. It's time the American Med-
l Association and state and local
edical societies paid off the debt by
cisive action to hold down the cost
medical care."

st of Drugs

Insurance rates and hospital
arges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned*. Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

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30 drugs that he selects to treat the
ajority of conditions encountered in
s practice. Moreover, the physi-
an's choice of a specific brand is
ised on his knowledge of the pa-
nt's medical history and current
ndition, and his experiences with
e particular manufacturer's
oduct.
Some substitution proponents
ve argued that the dispensing of a
escription is a simple two-party
ansaction between the pharmacist
id the patient, and that a substitut-
g pharmacist may avoid even a
chnical breach of contract by simply
otifying the patient that he is making
e substitution. I would judge that
w courts would be sympathetic
ward a pharmacist who substituted
ithout physician approval and who
idertook a legal defense that seeks
make the patient responsible for
e pharmacist's actions.

educed Prescription Prices?

Substitution advocates are
uggesting to the consumer, and par-
cularly the consumer activist, that
educed prescription prices could
ollow legalization of substitution.
/e have seen absolutely no evidence
justify this claim. To the contrary,
xperience in Alberta, Canada, where
ubstitution is authorized, suggests
the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands—of, say, ampicillin or tetracycline—or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

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Manufacturers Association
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Washington, D.C. 20005

P·M·A

The Rx that says "Relax"

BUTISOL Sodium provides highly predictable sedative effect: minor dosage adjustments are usually all that's needed to produce the desired degree of sedation. (With 3 dosage forms and 4 strengths to make adjustments easy.)

BUTISOL Sodium offers prompt, smooth, relatively non-cumulative action: begins to work within 30 minutes...yet, because of its intermediate rate of metabolism, generally has neither a "roller-coaster" nor a "hangover" effect.

BUTISOL Sodium is remarkably well tolerated: a 30-year safety record assures you that there is little likelihood of unexpected reactions.

BUTISOL Sodium saves your patients money: costs less than half as much as most commonly prescribed sedative tranquilizers.*

These are four good reasons for prescribing BUTISOL Sodium for the many patients who need to have the pace set just a little slower. Its gentle daytime sedative action is often all that's needed to help the usually well-adjusted patient cope with temporary stress.

*Based on surveys of average daily prescription costs.

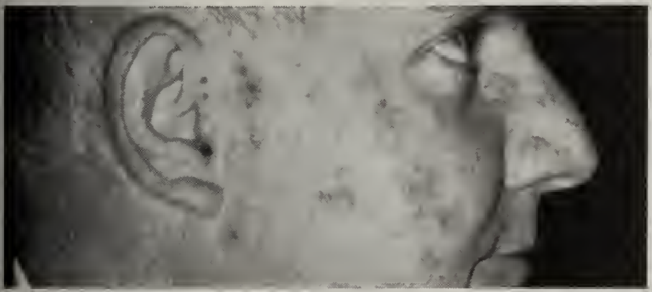
Butisol SODIUM®
(SODIUM BUTABARBITAL)

Contraindications: Porphyria, sensitivity to barbiturates, or susceptibility to dependence on sedative-hypnotics. **Warning:** May be habit forming. **Precautions:** Exercise caution in: moderate to severe hepatic disease; withdrawal in drug dependence or the taking of excessive doses over a long period, to avoid withdrawal symptoms; elderly or debilitated patients, to avoid possible marked excitement or depression; use with alcohol or other CNS depressants, because of combined effects. **Adverse Reactions:** Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and gastrointestinal

The lesions on his face may be solar/actinic—so-called senile" keratoses...and they may be premalignant.

Solar, actinic or senile keratoses

These lesions may be called by several names, but they usually can be identified by the following characteristics: the typical lesion is flat or slightly elevated, of a brownish or reddish color, papular, dry, rough, adherent, and sharply defined. They commonly occur as multiple lesions, chiefly on the exposed portions of the skin.



Patient P.T. seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.*

Sequence of therapy/ selectivity of response

After several days of therapy with Efudex® (fluorouracil), erythema may begin to appear in the area of the lesions; the reaction usually reaches its height of unsightliness and discomfort within two weeks, declining after discontinuation of therapy. This reaction occurs in affected areas. Since the response is so predictable, lesions that do not respond should be biopsied.

Acceptable results

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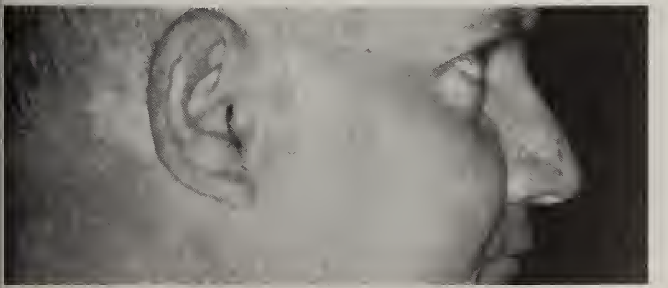

Patient P.T. seen on 6/12/67, seven weeks after discontinuation of 5%-FU cream. Reaction has subsided. Residual scarring not seen except for that due to prior*

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Indications: Multiple actinic or solar keratoses.
Contraindications: Patients with known hypersensitivity to any of its components.
Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.
Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.
Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.
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Acute Pancreatitis with Extensive Peripheral Fat Necrosis Simulating Erythema Nodosum and an Abdominal Cyst

WILLIAM O. DOBBINS III, M.D.*, MARTIN S. LIBERMAN, M.D.†

Abstract

Less than 20 patients have been reported with extensive subcutaneous fat necrosis simulating erythema nodosum associated with acute pancreatitis. This report documents, for the first time, the presence of a cystic right lower quadrant abdominal wall mass containing necrotic fat and requiring surgical drainage in such a patient.

Introduction

Reports of acute pancreatitis with skin lesions resembling cellulitis or erythema nodosum are infrequent.[1-6] Lipase release from the pancreas has been postulated as the mechanism of extra-pancreatic fat necrosis but available reports have rarely included serum lipase results and those reported have been normal.[1,2,3]

This report documents in the same patient extensive subcutaneous fat necrosis simulating cellulitis and erythema nodosum associated with an elevated serum lipase. Further, the patient developed a right lower quadrant abdominal extraperitoneal cyst-like mass, apparently the result of fat necrosis, requiring surgical drainage.

Case Report

A 50 year old alcoholic male was admitted to the Washington, D.C. VA Hospital on March 12, 1970 with abdominal pain and swelling. Six years earlier, he had been admitted for treatment of alcoholism and ascites. Two and one-half years previously, he was admitted with hepatomegaly, and a liver biopsy showed portal cirrhosis. A serum amylase then was 76 Somogyi units. Two weeks prior to admission, following heavy alcoholic intake, he developed anorexia and a dull constant pain between the scapulae which radiated to the right abdomen. The pain was relieved by the knee-chest position. He then noted midepigastric pain radiating to the back, abdominal swelling, and a nonpruritic eruption over the suprapubic area. He developed chills and fever and on admission there was progression of the rash over his abdomen, and he noted severe pain in his right inguinal region on sitting upright. There was no hematemesis, melena or joint pain. There were no known allergies.

On admission, he had a temperature of 37.8C, pulse of 100, and blood pressure of 110/80. He was thin with sunken cheeks and had evidence of generalized muscle wasting. The abdomen was asymmetrical, distended on the right, and was diffusely tender without rebound. There was a fluid wave, and bowel sounds were decreased. Liver span was 14 cm to percussion in the midclavicular line. There was an erythematous, blanching, tender, indurated 8 cm wide, band-like eruption of the right flank, extending from below the costal margin to the right suprapubic area (Fig. 1). Along the right flank and across the epigastrium were multiple raised, erythematous, blanching, non-tender, indurated nodules 1–2 cm in size (Fig. 1).

Laboratory Data

On admission the hematocrit was 42%, white blood count 18,000/cmm, with 81 neutrophils, 11 lymphocytes, three monocytes and five basophils. Platelet count was 306,000/cmm. The blood urea nitrogen was 10 mg/100

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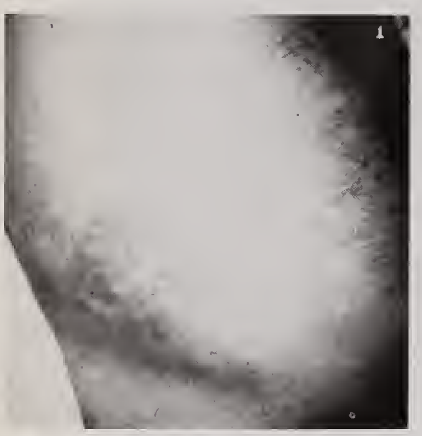

FIG. 1. Photograph showing indurated area in right flank of the patient over which can be seen multiple, slightly raised, erythematous nodules. The dilated venous pattern of the abdominal wall can also be seen.

ml; sodium 133 mEq/L; potassium, 4.8 mEq/L; and total bilirubin 0.7 mg/100 ml. Urinalysis was normal. The prothrombin time was 14.5 seconds with a control of 12.0 seconds. The total serum protein was 6 g/100 ml, with an albumin of 1.7 g/100 ml; the serum alkaline phosphatase was 19.5 K-A units. The serum amylase was 1500 units (Somogyi) and the 24-hour urine amylase excretion was greater than 3800 units/hour. The serum lipase was 5.9 units (Tietz-Borden) five days post-admission (normal 0–1 units). The serum cholesterol was 140 mg% and serum triglycerides were 102 mg%. The chest was normal without evidence of pleural effusion or hilar adenopathy. A barium study of the upper gastrointestinal tract showed large gastric folds, a finding confirmed at gastroscopy.

Hospital Course

An initial diagnosis of cellulitis of the abdominal wall was considered, and the patient was treated with oral penicillin after appropriate cultures had been taken. The penicillin was discontinued after two days when the cultures grew only coagulase negative staph aurens. Because of the striking elevation of the serum amylase, nasogastric suction and intravenous fluids were also begun.

The day after admission, papular circular indurated erythema nodosum-like lesions 1-2 cms in diameter were noted over the legs. A skin biopsy of an extremity lesion was obtained and demonstrated minimal subcutaneous fat necrosis; while a punch biopsy of the abdominal lesion revealed advanced subcutaneous fat necrosis with calcification. Two days later, the patient developed erythema nodosum-like eruptions over the arms. The extremity lesions cleared after two and one-half weeks. The abdominal induration persisted in the right lower quadrant and suprapubic area though the erythema disappeared.

By four weeks, there had been considerable decrease in the ascites with an associated 20 pound weight loss. However, the right lower quadrant abdominal mass increased in size. An IVP was normal but a barium enema revealed a homogenous soft tissue density displacing the right colon medially and posteriorly (Fig. 2).

Six weeks after admission, abdominal exploration through a transverse incision in the right lower quadrant revealed a walled off area between the transversus muscle fascia and peritoneum; and which contained approximately 1500 cc of milky colored fluid and a considerable amount of necrotic tissue. There was no connection to the pancreas. Microscopic examination of the material revealed irregular fragments of necrotic fat containing lipid crystals and degenerated amorphous material. The lesion was drained with two large Penrose drains. Cultures and cell block of this material were negative. An amylase of the material was 125 Somogyi units. The patient's postoperative course was uncomplicated, the lesion stopped draining two days after surgery and the serum amylase at that time was 83 Somogyi units and a urine amylase was 156 units/hour.

Discussion

The occurrence of fat necrosis in the pancreas and surrounding omentum and mesentery is common in acute pancreatitis, but fat necrosis involving areas distant to the pancreas is unusual.[3] There are less than 20 cases reported of this latter association. Szymanski and Bluefarb reported raised erythematous 1-2 cm diameter cutaneous nodules as a peripheral manifestation of acute hemorrhagic pancreatitis and adenocarcinoma of the pancreas.[4] Three of their five patients had painless lesions which appeared first on the lower extremities and subsequently on the trunk and upper extremities. The rather wide distribution of skin lesions in our patient helped differentiate them from the "usual" leg and forearm localization of erythema nodosum.

The essential histologic changes in subcutaneous fat necrosis occur only in the subcutis while there is usually no involvement of the epidermis or dermis. The foci of fat necrosis are characterized by ghost-like cells having thick walls and no nuclei.[4] No other disease involving subcutaneous fat tissue resembles this picture. In nodular non-suppurative panniculitis there is no fat necrosis[4,5] and, in erythema nodosum, the surrounding epithelioid and lymph cells produce a granuloma.[4]

Our patient is the first reported to have an elevated serum lipase concomitant with subcutaneous fat necrosis. Szymanski and Bluefarb have postulated that trypsin and lipase liberated into the circulating blood could produce disseminated foci of fat necrosis.[4], The trypsin has been thought to alter the cutaneous vessels and the circulating lipase has been thought to produce the fat necrosis.

Lipase hydrolyzes neutral fat to glycerol and free fatty acids, which then may react with ionizable plasma calcium, to form calcium soaps, and subsequently subcutaneous nodules.

Other authors postulate that disseminated fat necrosis is caused by lipase transported by other routes. Opie hypothesized that lipase was carried via lymphatics to sites of necrosis in the abdominal and thoracic cavities.[7] Perry produced intraperitoneal fat necrosis with pancreatin in rats and demonstrated fat necrosis along lymphatics draining the areas of necrosis.[7] In contrast, Popper and Necheles concluded that the increase of blood amylase and lipase following pancreatic injury was due mainly to the inflow of pancreatic enzymes into the general circulation by way of the portal vein and to a smaller extent by the flow of lymph through the thoracic duct.[8] Further, they wondered whether the passage of enzymes through the liver might be the cause of changes in the liver frequently found in acute pancreatitis.[8] Cummins and Bokus noted lipase elevations in approximately one third of their patients with cirrhosis in the absence of gross evidence of pancreatic disease.[9] Two of Swerdlow's patients with high serum amylase and subcutaneous fat necrosis also had evident liver disease,[1] as did the patient reported by Mayoral.[5] In our patient, liver disease clinically antedated the pancreatic involvement. It is conceivable that the associated liver disease may have somehow contributed to the persistent lipase elevation.

Our patient represents the most extensive degree of peripheral fat necrosis in pancreatitis yet reported and the first patient developing a cyst-like abdominal wall mass resulting from the process. This actually represented an area of necrotic extra-peritoneal fat in the right lower quadrant abdominal wall requiring surgical drainage. It was not a pancreatic pseudocyst in the usual form in that it was totally separate from the pancreas.

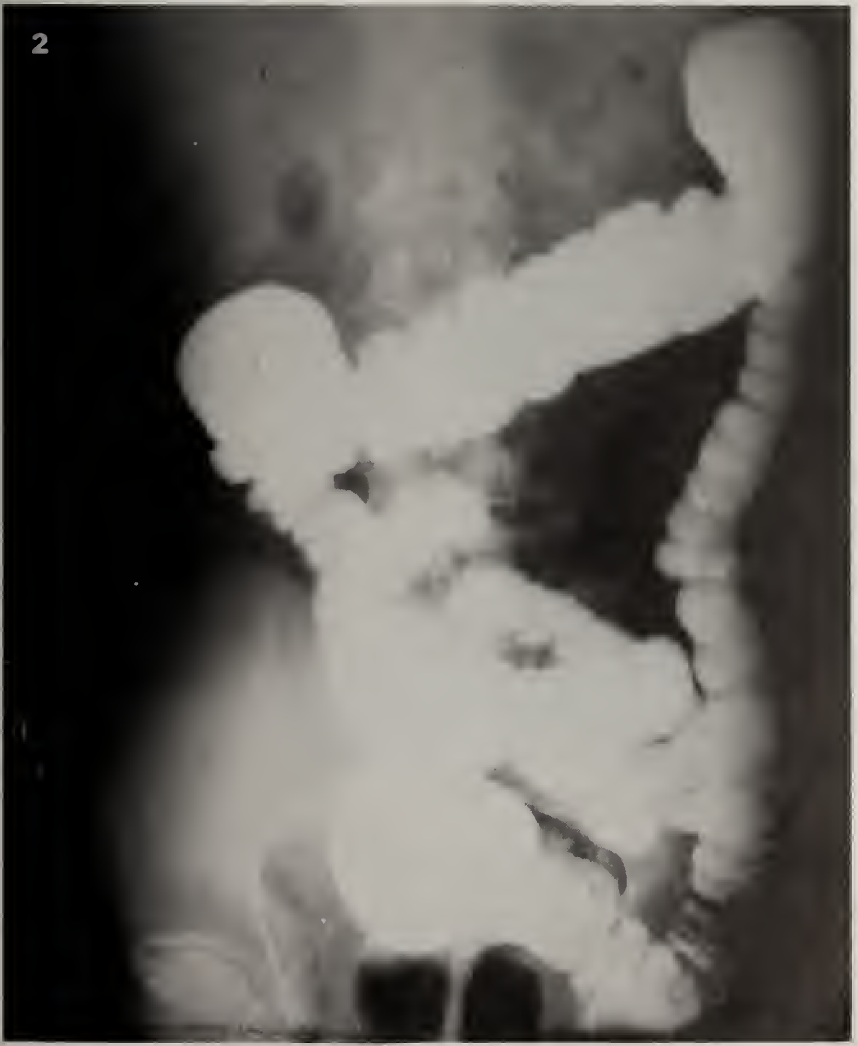

FIG. 2. Barium enema which illustrates the presence of a soft tissue mass displacing the right colon medially in this view.

Acknowledgements

We are indebted to Dr. William E. Reefe, formerly Chief, Medical Service, Veterans Administration Hospital, for the use of the photos of the abdominal and skin lesions.

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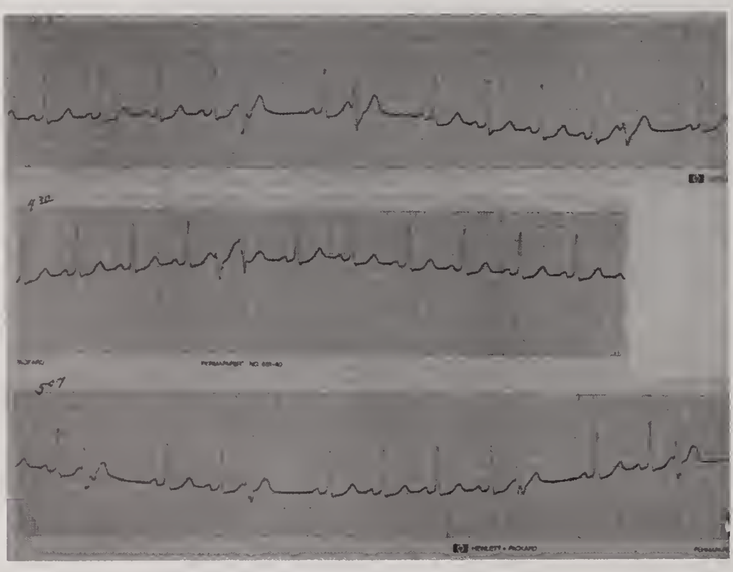
ECG Problems

HISTORY: 52-year-old man with acute myocardial infarction on March 15, 1973. Recovery was uncomplicated, but the patient complained of occasional sensation of skipped beat. None recorded on electrocardiogram or auscultation. These are representative samples from 12-hour Holter monitoring. Patient was asymptomatic during the study.



ECG Diagnosis

INTERPRETATION: 1. Ventricular premature beats with repetitive firing.

Several premature beats are shown. The basic contour of the QRS in all these beats is essentially the same, suggesting that they come from a single focus. In the second strip, there is repetitive firing with two ectopic beats in a row. Most of the others are placed relatively near to the T wave of the preceding beat, the so-called "vulnerable zone." Ventricular premature beats which are so placed, and those which occur repetitively as in the second strips are viewed as dangerous, predicting the possible onset of ventricular tachycardia. A few hours later, several brief bursts of ventricular tachycardia did occur.

Edited by Robert R. Montgomery, M.D.

Estimation of the Number of Narcotic Addicts in an Urban Area

ROBERT L. DUPONT, M.D.*, THOMAS E. PIEMME, M.D.†

Abstract

No precise reliable method exists for the estimation of the number of heroin addicts in urban areas. A formula devised by Dr. Michael Baden of New York City, based upon the rate of overdose deaths, has gained some acceptance; but applicability depends upon a high degree of sophistication within the Medical Examiner's Office, and may well not be applicable outside New York. Application of the formula to Washington, D.C. yields an estimate of 17,700 addicts in the Capital.

A new method of estimation, analogous to biologic dilution techniques, is described based upon prior registration of addicts with the Narcotics Treatment Administration of the District of Columbia. Calculations based upon this method and applied to three different subsets of the addict population of the city yielded remarkably similar estimates of 20,000, 20,400, and 19,900 addicts in Washington. These considerations are critical to the proper evolution of public policy and resource allocation.

Introduction

Almost all American cities are reporting an alarming increase in the use of heroin as well as increases in crime and in disease associated with the culture of narcotic addiction. Addiction is defined as narcotic dependency requiring daily drug use in order to prevent symptoms of narcotic withdrawal. Addicts are identified and apprehended, overdoses reported, illness managed, and treatment centers opened, yet the magnitude of the problem eludes precise definition. Most authorities would agree that addicts processed by the criminal justice system and those in voluntary treatment programs represent but a fraction of the addict population.

The issue is critical. Within the District of Columbia, a city of 756,500, estimates of the number of heroin-dependent persons have ranged from an unrealistic 1,743 to an equally preposterous 60,000. The numbers game is played vigorously by special interest groups, some of whom would like to inflate the problem while others would like to deny it. Major issues of public policy are at stake. Accuracy is critical for resource allocation and for program planning at the national, state, and local levels.

Unfortunately, no simple reliable formula exists for estimating the number of addicts in any given geographic area. In Washington, D.C. the Narcotics Treatment Administration (NTA), an agency less than two years old, is attempting to determine the number of addicts by means of increasingly sophisticated formulae. It is possible that these techniques will prove useful elsewhere.

Background

In 1969, Washington had fewer than 100 heroin addicts in treatment. When public attention began to focus on the problem, the only figure relating the size of the addict population was a 1968 Federal Bureau of Narcotics and Dangerous Drugs (BNDD) count of 1,162 addicts in the District of Columbia. By 1970, the BNDD figure had risen to 1,743. No one, including BNDD, could credit these numbers as realistic estimates of the magnitude of heroin addiction in the community.

In February of 1970, the NTA was created as an agency charged by the District government with coordination of all narcotic treatment programs in the Capital, with the responsibility for the identification of the addict population, and with the mission of establishing effective treatment for the management of heroin addiction. Adequate planning demanded accuracy in the estimation of the numbers of ad-

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dicts who might be registered and treated.[1,2]

The Baden Formula

One well-known technique for estimating the number of addicts is based upon the number of heroin overdose deaths. Michael Baden, Deputy Chief Medical Examiner for New York City, found that in a one-year period there was one overdose death (see footnote 1) for each 200 individuals among the more than 50,000 registered heroin addicts in New York City.[1] Thus, the "Baden Formula" multiplied overdose deaths per year by 200 to estimate the size of the total addict population.

There is reluctance to apply the Baden Formula outside New York City for three reasons. First, many cities have primitive medical examiner systems that fail to identify all heroin-related deaths, thus underestimating the size of the total addict population. Second, cultural patterns among addicts differ somewhat from city to city in a manner that might influence the overdose death rate. Cluster occurrences, for example, underscore non-random distribution of deaths among addicts. Third, the concentration of street heroin purchased outside of New York City is likely to be different. Should dilution lead to decreased probability of death from overdose, the size of the addict population will be underestimated. Thus, any estimate based on the Baden Formula requires corroboration.

In mid-1969, the Coroner of the District of Columbia developed more extensive toxicologic capabilities and began to inspect sudden deaths more carefully for the possibility of opiate overdose. By July of 1970 the process had been systematized: all autopsies of deaths of individuals between the ages of 10 and 40 that came to the attention of the Coroner's Office included a screen for tissue concentrations of opiate derivatives and of quinine. 51% of autopsied deaths were surveyed in 1970–71 as opposed to six percent during 1969–70. There was a corresponding increase of detection of narcotic abuse. Whereas eight overdose deaths had been identified during the quarter ending June 30, 1970, 22 such deaths among narcotic users were identified in the subsequent quarter. Use of the Baden Formula after July of 1970 seemed justified. Between July 1970 and June 1971, 75 deaths were identified as attributable to heroin overdose. Multiplying this number by 200 and adding the result to the 2,700 addicts, (average) known to be in treatment (see footnote 2) through programs of the NTA over the same period, yielded an estimate for the District of Columbia of 17,700 addicts. Two questions now needed to be answered: 1) Was there indeed random distribution of overdose deaths among addicts so that *some* ratio was applicable? 2) Given randomness, was the 1:200 Baden figure applicable to the District of Columbia?

Beginning in the fall of 1970 all persons participating in the NTA program were initially registered at a central intake facility. A photograph was taken of the patient and he w
issued a numbered identification ca
which was used like a credit card to t
all patient services into the NT
computerized information system. B
October 1, 1971, 7,827 addict recor
had been entered into the system
Basic identification material (driver
license, birth certificate, or soci
security number) was required. Sinc
fingerprint identification was not ob
tained, it is possible that a few addic
may have registered more than onc
Moreover, a few suburban residen
may have given false D.C. addresses i
order to obtain treatment. Neverthe
less, duplicate registration of the sam
person and registration of suburba
residents were thought to involve onl
a small percentage of the total registry

Contrast was made between th
demography of overdose deaths an
the demography of patients on th
NTA registry. The comparison may b
seen in Table 1. The data correspon
remarkably well. There is no know
reason to believe that either set o
persons is other than a random sampl
of Washington's addict population
Non-random selection would have t
be biased by identical factors in th
two groups in order to achieve such
close correspondence. Thus, we were
persuaded that there did exist a ratio
of annual overdose deaths to addicts at
risk, although that ratio could well be
other than 1:200.

One by-product of the demographic
contrast approach was the capacity to
determine an upper limit to the number of addicts in the District. The
subset of the District population at
greatest risk was black males, 20 to 24
years of age, living in the Model Cities'
Neighborhood. Application of the
Baden ratio to this group revealed an
incidence of heroin addiction of 36%.
Since it is obvious that no more than
100 % of any subset of the population
are at risk, the maximum multiplier in
a Baden-type approach is 555. Thus,
there could be no more than 44,300
addicts in the District of Columbia.

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[1] An opiate overdose death is defined as an unexpected fatality, which after complete evaluation of the anatomic, toxicologic, and circumstantial evidence, is considered to be related to the use of an opiate drug. This definition excludes medical and social complications of addiction such as hepatitis, bacterial endocarditis, and gunshot wounds. It should be noted that the term "overdose" is a misnomer because the pathophysiology of heroin-related sudden death is unknown.

[2] Treatment would appear to protect against overdose death. Only four deaths via overdose have occurred among patients registered with NTA in two years. All four had been in the program less than two weeks, and by definition would not have been counted as under "treatment." In order to be counted, a minimum of two weeks compliance with a prescribed set of criteria is required.

Attempts to determine an accurate atio of overdose deaths to addicts at isk for the District of Columbia are rustrated by the absence of any sizeable existing list not predicated upon enrollment in a treatment program. A 1968 list of drug abusers kept by the D.C. Health Department contained 615 names. Three of these persons died of heroin overdose during 1970 yielding a ratio of one death per 205 addict-years. Two persons on a 1969 BNDD list of 970 names died of heroin overdose in 1970 implying one death per 485 addict years. These estimates are unreliable because of the few deaths involved. As the NTA registry grows larger, it should be possible to discern the overdose mortality rate among those registrants who do not remain in treatment in order to determine a more accurate multiplier. Meanwhile, the existence of the registry permits a new approach to the solution of the problem.

TABLE 1. Demographic Comparison of Overdose Death Rates with Addicts in NTA Registry

	Overdose Deaths %	Addicts in Registry %
Black	87	95
Male	76	80
21 Years	31	31
16–25 Years	65	59
Residence in Model Cities Neighborhood	28	24

An Indicator–Dilution Formula

In an attempt to estimate the number of heroin-dependent addicts in the District of Columbia, we used an approach similar to radioactive tagging of dispersed substances, or dilution of indicators into a volume pool. The indicator is the identification of prior enlistment into the NTA registry.

Between September 27 and October 13 of 1971 a total of 186 voluntary patients were taken into treatment in NTA facilities. 43 (23.1%) of these had previously registered but had dropped out of treatment. Assuming that addicts were presenting themselves for treatment at equal rates, regardless of whether they were in treatment previously, we may estimate the total untreated population by assuming that 23.1% of all addicts not in treatment during the study period had registered with the NTA but had dropped out of therapy. This number is known to be 3,679 (7,827 registered less 4,148 in the active treatment). Thus, 100% of the addict population not in treatment would be 15,900 persons. Adding to this number the number of addicts in treatment during the same period yields just over 20,000 total addicts in the District.

The D.C. Superior Court in April of 1970 began a joint program with NTA to screen all defendants for possible heroin addiction. Those identified as addicts and released to the community prior to trial were referred to the NTA for treatment. During September of 1971 there were 119 such persons—of whom 27 had previously registered with the NTA at some previous time but had dropped out of the treatment program. This number represented 22.7 % of referrals, a percentage comparable to the 23.1 % of self-referrals discussed above. Similar argument and calculation produced an estimate of 20,400 addicts in the District of Columbia.

In May 1971, a BNDD list of 1,225 active addicts was compared with the NTA registry which was then 5,292. 326 of these persons were in the registry. Assuming that prior registration was independent of later inclusion on the BNDD list (the NTA registry is not available to BNDD), calculation yielded an estimate of 19,900 addicts in the city.

The three estimates that result from application of this "indicator-dilution" technique are obviously based on a number of unproven assumptions. The origin of the three subsets is quite diverse. One set of persons is coming voluntarily for treatment; another represents a group caught up in the criminal justice system; the third represents persons who have come to the attention of BNDD. (The BNDD list is composed of names of known addicts submitted by the Police Department.) Each estimate is based on many observations. Nevertheless, none taken alone would be persuasive. Taken together, however, they cover a startingly narrow range somewhat larger than estimates derived from the Baden Formula.

Looking at the data somewhat differently, if there were 20,000 addicts in the District of Columbia in 1970-71 when there were 75 opiate overdose deaths, then the Washington ratio of overdose deaths to addicts would be 1:231 (assuming an average of 2,700 addicts in treatment during that time period).

Discussion

The estimates of the number of heroin-dependent addicts in the District of Columbia are summarized in

TABLE 2. Estimation of Number of Addicts

1970	BNDD List	1,743
1971	Baden Formula	17,700
	(upper limit)	(44,300)
1971	Dilution Method	
	Voluntary Treatment List	20,000
	Superior Court Screen	20,400
	BNDD List	19,900

Table 2. The figures, while generally similar, are crude. It is not yet possible to determine whether the addict population has changed during the past year. With only about 20% of the city's addicts in treatment, it is unlikely that the population size has decreased as a result of therapy. On the other hand, it is not unreasonable to expect that the treatment of one-fifth of the District's addicts may have been sufficient to stabilize the numbers after dramatic growth during the late 1960's. It may be significant that during the 12 months ending June 30, 1971, there was a modest decrease in the overdose death rate. Quarterly figures were 22, 19, 19, and 15. However, the quarter ending September 30, 1971, saw 25 overdose deaths.

On the basis of currently available data, it appears that there are about 18,000 to 20,000 addicts in Washington, D.C. It also appears that the size of the addict population has not changed markedly during the 15 months ending September 30, 1971. The fact that there may not have been a large increase in the addict population during this period may make Washington unique among the nation's larger cities.

Much more remains to be learned about the size, composition, and development of heroin addict populations. The continued growth of the NTA addict registry will permit increasingly reliable judgments on the many critical unanswered questions. Meanwhile, this current effort at estimating the population of addicts should be considered an interim step between almost total ignorance and firm knowledge.

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Hypercalcemia During the Diuretic Phase of Acute Renal Failure

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AND ALVIN E. PARRISH, M.D.[‡‡]

Introduction

Hypercalcemia occurring during the diuretic phase of acute renal failure has previously been reported in nine patients (Table 1). These cases are briefly reviewed, with the reporting of another patient and speculation on the mechanism of the hypercalcemia.

Report of Case

T. H., a 20 year old white man, was admitted to the George Washington University Medical Center Hospital on June 13, 1972 for treatment of acute renal failure. He had a one and one-half month history of intravenous heroin use and was initially admitted to a neighboring hospital after an acute overdose of heroin, combined with alcohol ingestion, resulted in a prolonged period of coma. Oliguria and hyperkalemia were noted and treated with sodium polystyrene sulfonate resin, calcium gluconate, and intravenous dextrose with insulin. He was then transferred to another neighboring hospital for hemodialysis, where marked swelling of the left arm and leg were noted. One peritoneal dialysis and three hemodialyses were performed, then he was transferred to the George Washington University Medical Center. His past medical history had been unremarkable; prior to his present illness he had been employed as a construction worker. His pre-illness weight was 186 lbs.

On admission his blood pressure was 130/80 mm Hg., temperature 38°C, pulse 90 and regular, and his weight 220 lbs. An A-V shunt for hemodialysis was present in his right arm. The left arm appeared warm, edematous, and tender with severely limited range of motion. There was edema of the left chest wall, scrotum, penis and legs, and he complained of frequent cramps in his left leg. A papulovesicular rash was noted on the left arm and leg. The physical examination was otherwise unremarkable.

His urine on admission contained 2+ protein and blood. Brown pigmented casts were noted which completely absorbed ultraviolet radiation (i.e. appeared black against a blue background) when examined via a Soret filter. Aside from the probable hemoglobin casts, the urine contained 50–100 RBC/HPF and WBC TNTC/HPF with numerous renal tubular cells/HPF. Cellular casts were also noted but no RBC casts were seen. The urine was negative for myoglobin on immunoelectrophoresis.

As the question of possible inferior vena caval or renal vein thrombosis had been raised at the referring hospital, an inferior venocavogram was performed on June 15 and was negative.

The patient was maintained at bed rest during most of the hospital course, due to his leg symptoms.

Hemodialysis was performed on June 14, 16 and 19 using double Extracorporeal^{R} EXO3 coils and a standard commercial dialysate with a final calcium concentration of 2.5 mEq/l. (not including the variable

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TABLE 1

Date	Urine Volume (ml.)	BUN mg/100ml.	Creatinine mg/100ml.	Ca/P mg/100ml.	Ca x P Product	Alkaline Phosphatase mu/ml.	SGOT/LDH mu/ml.	CPKu%	Total Bilirubin mg/100ml.
6/3-12	100–200	30–111	Rose to 7				4000/1200		0.9–1.0
6/13	250	123		7.5/7.7	58				
6/15	250								
6/16	450								
6/17	500								
6/18	1170								
6/19	480								
6/20	1610								
6/21	1780	63	8.9	11.4					
6/22	3510	108							
6/23	3820	111							
6/24	INC	120		11.9/8.1	96	63	58/367		
6/25	INC	112							
6/26	INC	87		13.2/6.7	88				
6/28	2450	61	2.8	13.9/5.6	78	78	42/268		
7/2	3850	33	1.8	11.9/3.5	42				
7/4	2750+	29	1.6	11.6/3.4	39	134	111/234		
7/7		22	1.2	9.8/3.9	38	202	450/305	27	0.6
7/9		18		10.0/3.6	36	179	112/238		0.4
7/13		18	0.9	9.6/3.5	34	157	40/173		0.6
7/19		17	0.9						

Normal values

Ca–8.5–10.5 mg/100 ml.
P–2.5–4.5 mg/100 ml.
Total bilirubin–0.2–1.0 mg/100 ml.
Alkaline Phosphatase–< 85 mu/ml.
SGOT–< 50 mu/ml.
LDH–< 200 mu/ml.
CPK–< 20 u%

amount of calcium in the tap water added to the concentrate).

Three days after admission, the urine output rose to 450 ml/24 hours. After a week the urine output was 1780 ml/24 hours, and the serum calcium was 11.4 mg/100 ml. (normal 8.5–10.5 mg/100 ml.). The serum calcium rose to 13.9 mg/100 ml. on the 14th hospital day, at which time the 24 hour urine volume was 2450 ml. (See table 1), and the serum creatinine had fallen to 2.8 mg/100 ml. from a high of 8.9 mg/100 ml. on June 21, 1972. The alkaline phosphatase became elevated six days later to 134 mu/ml. (normal less than 85 mu/ml.)

Bilateral scleral injection was first noted on the ninth hospital day and disappeared slowly. The serum calcium fell toward normal as diuresis continued, reaching 9.8 mg/100 ml. on the 31st hospital day. At this time the serum creatinine was 1.2 mg/100 ml. and the creatinine clearance was 79 ml/min.

The LDH and SGOT were elevated initially, presumably secondary to muscle trauma, but the reason for the late elevations is unclear.

Discussion

Hypercalcemia associated with the diuretic phase of acute renal failure has been reported in nine patients,[1–9] and was noted in this patient. Seven of the previously described nine cases were associated with renal failure associated with muscle injury, myopathy or myoglobinuria.[4] In four of these cases, the hypercalcemia appeared before the onset of the diuretic phase, and in the other five and in the present case it appeared after the onset of diuresis. Two patients have been reported where the hypercalcemia was

TABLE 2. Case Comparisons

Case No.	Author	Specific Diagnosis*	Related Conditions	Muscle Calcification	PTH Assay+	Alkaline Phosphatase
1	Tavill, 1964	Idiopathic Paroxysmal Myoglobinuria, Acute Tubular Necrosis				
2	Segal, 1968		Burns, Ischemic Pressure Myopathy Right Thigh			
3	Butikofer, 1968		Ischemic myopathy	+		
4	Turkington, 1968					>1–2 days after onset of hypercalcemia
5	Turkington, 1968	Acute Tubular Necrosis			PTH > during hypercalcemic phase	>1–2 days after onset of hypercalcemia
6	Grossmann, 1968		Extensive crush injury to muscle left arm	+		
7	Leonard and Eichner, 1970	Idiopathic Rhabdomyolysis, Acute Tubular Necrosis			PTH > during hypercalcemic phase	Elevated
8	Leonard and Nelms, 1970	Heat stroke with exertional rhabdomyolysis, Acute tubular necrosis				
9	Grunfeld, 1972	McArdle's Disease				Elevated
10	Present case		Muscle trauma	Not Documented	No	Elevated late

Case No.	Enzymes‡	Onset of hypercalcemia relative to diuretic phase	Pre & Post Hypercalcemia dialysis experience	Lowest serum PO_4 mg/100ml.	Ca x P Product	Conjunctival Reaction (N.D. = No Data)
1	Elevated	Before	Hemodialysis x 1 prior to hypercalcemia H.D. x 1 post $\bar{c}$ ↓ Ca bath	2.5	157.5	+
2		After	Peritoneal dialysis x 3, demodialysis x 1 prior to ↑ Ca	2.5	84.5	ND
3		Before	None			ND
4		Before (Maximal elevation after onset of diuresis)	None	2+		ND
5		Before (Maximal elevation after onset of diuresis)	Intermittent peritoneal dialysis prior to hypercalcemia	3±		ND
6		After		1.9		ND
7	↑ CPK	After	Hemodialysis x 4 prior to ↑ Ca, Bath Ca 2.7 mEq/l.	3.1	102.4	+
8		After	None			+
9	↑ SGOT, LDH, SGPT, CPK	After	P.D. x 1, H.D. x 7 prior, bath Ca not specified. H.D. x 2 post, Bath Ca not spec.	<3	167	+
10	↑ SGOT, LDH SGPT, CPK	After	Pre & Post hypercalcemia	3.4	96 (Max.)	+

* All cases of acute renal failure, specific diagnosis of precipitating condition and by renal biopsy.

† PTH = Parathormone.

‡ SGOT, LDH, CPK.

associated with resorption of extraosseous calcification in injured muscle (cases three and six).

The etiology of the hypercalcemia remains unclear. Hypercalcemia secondary to immobilization has been suggested by Tavil,[1] but as shown by Heath, et al,[9] this appears within four to five days of bed rest and is primarily an increase in the ionized fraction, with little change in the total calcium level in individuals with normal renal function. If immobilization were the primary etiological factor, one might expect the calcium to be highest when the renal function was the poorest, rather than in relation to the diuretic phase when renal function is rapidly improving. Also, previous case reports have not consistently detailed the degree or duration of bed rest, making impossible a retrospective judgment on the role of immobilization.

Resorption of calcium from ectopic calcifications in traumatized muscle has been suggested as an etiology of the hypercalcemia,[3,5] with the assumption that as renal function improved, the ectopic calcium was mobilized and ultimately excreted.

Finally, hyperparathyroidism secondary to the renal failure has been suggested as important in the etiology of the hypercalcemia.[2,5,6,7] Where parathyroid hormone had been measured, however,[4,6] the results have been variable.

In the two cases where alkaline phosphatase evaluation has been mentioned relative to the onset of hypercalcemia,[4] it occurred one to two days after the onset of the calcium elevation, and on the 13th day in the present case.

It has been demonstrated that with renal failure Vitamin D metabolism is impaired,[10] with a decreased formation of the active form of Vitamin D (1-25 dihydroxycholecalciferol) by the renal parenchyma and subsequent decreased Vitamin D effect including impaired gastrointestinal absorption of calcium. This results in hypocalcemia with subsequent parathyroid stimulation. When the renal parenchyma begins to recover, (as shown by improved renal function) one can hypothesize that as the rate of conversion of Vitamin D to the active metabolite 1-25 dihydroxycholecalciferol increases; the effects, of the resultant increased effective Vitamin D levels along with the elevated parathormone level, would lead to an elevation of the calcium level and even to hypercalcemia until the parathyroid activity had again been suppressed. A similar phenomon has been noted after renal transplantation.[11]

Summary

Hypercalcemia was noted during the diuretic phase of acute renal failure associated with muscle injury. It is postulated that secondary hyperparathyroidism developed during the episode of renal failure; and as Vitamin D metabolism improved during recovery a transient period of hypercalcemia may have developed with subsequent parathyroid suppression and return to a normocalcemic state.

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Hepatitis Virus B Infection in an Alcoholic with Cirrhosis

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Introduction

This communication represents the first reported case of documented Australia antigen (Hb Ag, hepatitis B) positive hepatitis following transfusion in an alcoholic patient with cirrhosis. It points out the paucity of controlled studies concerning the incidence of transfusion related hepatitis in alcoholics, a population in which there is a high incidence of gastrointestinal bleeding requiring blood transfusion. There are almost no studies of patients with alcoholic cirrhosis in regard to the incidence of Australia antigen positive hepatitis, and the role this may play in development of cirrhosis. The physician should be alerted to the possible concurrence of both hepatitis B disease and alcoholic liver disease in the same patient as illustrated in the following case report.

Case Report

The patient, a 65 year old white male, was admitted to George Washington University Hospital on September 14, 1972 to evaluate a week's history of jaundice, weight loss, malaise, dark urine, and light colored stools. He had a 45 year history of heavy alcohol ingestion with documented abnormal liver function tests in the 1950's including a BSP of 10% and a transaminase (SGOT) of 48.5 sigma units (normal to 40). In 1967 he had an appendectomy and the surgeon described the liver as "normal sized but indurated and with the diffuse nodularity characteristic of cirrhosis". At this time, the bilirubin was 2.7 mg%, SGOT 214 I.U. (normal to 40), alkaline phosphatase 26 Bodansky units, prothrombin time 18.3 seconds with a control of 11.3 seconds, albumin 3.7 g%, and globulin 4.2%. In 1968, following a mild hematemesis, the patient was admitted to GWUH and a barium swallow was reported as "suggestive" of esophageal varices. The bilirubin was 3.4 mg%, prothrombin time 18 seconds with a control of 13 seconds, and the BSP was 27%.

In May 1972, he was again admitted because of massive upper gastrointestinal bleeding. At esophagoscopy, large esophageal varices were noted along with a probable Mallory-Weiss tear on the gastric side of the esophagogastric junction. Laboratory values revealed an albumin of 2.6, alkaline phosphatase of 79 I.U. (normal to 85), and SGOT of 156 I.U. He required six units of fresh frozen plasma, four units of whole blood, and 15 units of platelets during initial treatment. He developed deep hepatic coma on the second hospital day but recovered uneventfully with appropriate therapy. After discharge, he faithfully attended AA meetings and ceased alcohol intake. (This history was verified by all members of the family.)

At the final admission on September 14, 1972, his temperature was 37.6°C, pulse 96 and regular, and respirations 18. Blood pressure was 140/80. Positive physical findings included a skin with a deep yellow tinge, numerous spider angiomas and palmar erythema of both hands, the latter two having been observed on earlier admissions. The sclera were icteric. Course rhonchi were present throughout the lungs and there was an increased A-P diameter of the chest. The liver span was percussed at seven cm in the midclavicular line. The spleen was not palpable and there were no ascites or ankle edema. The testes were small and soft and the stool was yellow and guaiac negative. He had loss of sensory and position sense in the distal lower extremities, and a wide-based gait. He was mentally alert and gave a clear history. Laboratory data during the admission are recorded in Table 1.

His hospital course was progressively downhill with a marked decline in his mental status and development of asterixis. Treatment included low protein intake, neomycin enemas, oral neomycin and 400 mg hydrocortisone every 8 hours. Deep coma developed

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requiring nasotracheal intubation. He developed cardiopulmonary arrest on the tenth hospital day and could not be resuscitated. At postmortem, the liver weighed 1150 gm and showed micronodular cirrhosis with marked cholestasis and no fatty infiltration. The cut surface revealed irregular parenchymal nodules measuring 1–5 mm in size. There was a striking paucity of morphologic changes of hepatitis with no cellular infiltration and no necrotic liver cells.

Discussion

Jaundice in the cirrhotic patient may result from a variety of complications superimposed on the already diseased liver, i.e. alcoholic hepatitis, chronic active hepatitis, hepatoma, drug toxicity, or extra-hepatic biliary obstruction. There are few reports of possible serum hepatitis complicating Laennec's cirrhosis. Popper and Ducci stated in 1957 that they had never observed Laennec's cirrhosis with concommitant morphologic signs of viral hepatitis.[1,2]

In 1960, Wenger et al presented an alcoholic with biopsy-documented Laennec's cirrhosis who died, 60 days after a blood transfusion, with increasing serum bilirubin, decreasing serum albumin, and increasing serum prothrombin time, all suggestive of acute viral hepatitis.[3] Postmortem liver sections revealed cirrhotic changes and necrosis of virtually all liver cells.[3]

In 1967, Eschar et al published reports of seven cases of probable post-transfusion hepatitis during the course of alcoholic cirrhosis.[4] All patients had a marked rise of the SGOT to values between 500–1000 units during the episode of jaundice. The SGPT values were elevated but less than the SGOT values.

In all forms of alcoholic liver injury (cirrhosis, fatty metamorphosis, and fatal and non-fatal steatonecrosis) the SGOT:SGPT ratio is usually greater than 1.0 with the SGOT usually in the range of 50–300 I.U.[5] In contrast, in viral hepatitis and in other wide-spread necrotic processes of the liver, the SGOT values are above 300 I.U. and usually greater than 1000 I.U. with even higher SGPT values.[4,5] It is interesting to note that in the Eschar case and in our case, the SGPT value remained much lower than the SGOT. This transaminase pattern may be a clue to the entity of viral hepatitis superimposed on pre–existing alco-

TABLE 1. Laboratory Values

Date		9/14	9/18	9/20	9/22	9/23
BUN	mg%	13	28	51	84	105
Creatine	mg%				6.7	
Cholesterol	mg%	221	226			208
Ttl. Protein	g%	7.7	7.2			6.5
Albumin	g%	2.1	1.7			1.2
Ttl. Bilirubin	mg%	50	30			31
Alk. Phosphatase	I.U.	182	136			99
SGOT	I.U.	1500	1050			233
SGPT	I.U.	390	230			
Na	mEq/L	136		128	137	
K	mEq/L	3.0		4.6	4.3	
CO2	mEq/L	25		16	15	
Cl	mEq/L	100		96	92	
Urine Na	mEq/24 hrs.	125	19	30		
Urine K	mEq/24 hrs.		72	61		
Hct		37.3			34	
Hb	mg%	12.5			11	
WBC		6700				
Differential		78 segs, 2 bands, 14 lymphs, 5 monos, 1 eos				
Alpha fetal globulin		negative				
Platelet count		101,100				
Prothrombin time		23/12 seconds				
Partial thromboplastin time		27.7/36.4 seconds				
Australia antigen		positive (counter current electrophoresis)				
Liver scan		abnormal liver scan suggesting fibrotic nodular cirrhosis with moderate portal hypertension-increased spleen and marrow uptake				

holic cirrhosis. The occurrence of jaundice and transaminase levels greater than 500 I.U., two weeks to 6 months after infusion of blood, may be considered presumptive evidence of post-transfusion hepatitis. The liver biopsies in the cases of Eschar were consistent with but not diagnostic of viral hepatitis. Popper[1] suggested that it is likely the histologic patterns of cirrhosis obscure the acute changes of viral hepatitis. This may explain the striking lack of morphologic evidence of hepatitis in the postmortem sections of liver in our patient.

Our patient had a long history of grossly excessive alcohol intake with a characteristic appearance of cirrhosis of the liver being noted at earlier surgery. He had upper gastrointestinal bleeding with documented varices and a Mallory-Weiss tear requiring whole blood, platelets and fresh frozen plasma transfusions. Four months later he was admitted with classic signs and symptoms of serum hepatitis. SGOT and SGPT values were greatly elevated and postmortem liver biopsy showed micronodular cirrhosis. Australia antigen was present in his serum. It is likely that he had alcohol associated cirrhosis of the liver and that he developed serum hepatitis related to an Australia antigen contaminated blood transfusion. It is far less likely that he had chronic Australia antigenemia (not tested for prior to his last admission) with chronic active hepatitis and a terminal exacerbation of the hepatitis. All liver function tests had been most compatible with alcohol associated liver disease, not chronic active hepatitis.

Pettigrew et al found evidence of cell mediated immunity to hepatitis virus B (Australia antigen, Hb Ag) in all of 11 cases of alcoholic cirrhosis, and thus suggested that hepatitis virus B may be an etiologic factor in the development of alcoholic cirrhosis.[6] We do not agree with this conclusion because Cherubin et al have shown the incidence of antibody (Hb Ab) to Australia antigen (Hb Ag), and immunity increases with age and with lower socioeconomic status.[7] Presumably, alcoholic cirrhotics are more likely to be of low socioeconomic status. Thus evidence of cellular immunity to Hb Ag in alcoholics may mean only prior exposure.

The concurrence of hepatitis virus B in alcoholic cirrhosis is thought to be rare. However, there are no comparative studies using an age matched population and this clinical impression may not be valid. This possible association deserves close study from two view points (1) that prior exposure to hepatitis virus B protects alcoholic cirrhotics from subsequent clinical viral hepatitis, or (2) that the prior exposure to hepatitis virus B actually plays a role in the development of "alcoholic" cirrhosis.

Summary

The paucity of post-transfusion serum hepatitis among alcoholics with cirrhosis seems enigmatic. We report an additional presumptive example of this and the first in which the presence of Australia antigen was documented. It could be that alcoholic cirrhotic patients are protected from acute serum hepatitis because the cirrhosis is related to a combination of alcohol injury and prior infection by serum hepatitis. However, hepatitis in the alcoholic is usually presumed to be ethanol induced unless proven otherwise. Only in the last two to five years, with the availability of Australia antigen, has it been possible to prove otherwise. The entity of hepatitis among alcoholic cirrhotics requires further study as to the possible role of hepatitis virus in the etiology of alcoholic cirrhosis.

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Severe Multisystem Allergic Reaction to Sulfisoxazole

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Abstract

A case summary of an allergic reaction to sulfisoxazole manifested by skin eruption, toxic hepatitis and hemolytic anemia is presented. Lymphocyte stimulation studies confirmed the diagnosis of drug sensitization. One hundred thirteen cases of sulfonamide allergic reactions are discussed.

Introduction

Drug allergy and toxicity are becoming ever increasing diagnostic and therapeutic problems. Of 1,014 consecutive patients admitted to the Yale University Medical Service of the Grace-New Haven Community Hospital, 103 suffered adverse reactions to therapeutic drugs during their hospital stay.[1] A three month study conducted on the Resident Medical Service of the Johns Hopkins Hospital revealed that 5% of patients were admitted because of drug reaction. 30% of these patients acquired another reaction during hospitalization.[2] The economic consequences of drug reactions were studied by the Pharmacy Service of the Ohio State University Hospitals. They found that during a three month period the cost of diagnostic tests performed on patients admitted specifically because of a drug reaction was $11,258.[3]

Conventional laboratory tests were unable to confirm the diagnosis of drug allergy, to pinpoint the offending drug when several are being given to the same patient, and to differentiate between coincident disease and the manifestations of drug allergy such as viral hepatitis versus toxic hepatitis. Skin testing patients suspected of allergic drug reactions exposes them to the potential danger of unpredictable and sometimes severe systemic reactions. For all these reasons, it is important to have a reliable *in vitro* technique by which drug allergy may be diagnosed.

The sulfonamides are an ubiquitous class of drugs. They are used as antimicrobials, diuretics, and hypoglycomics. This case report presents a patient with an unusually severe multisystem allergic reaction to sulfisoxazole. It is intended to alert physicians to the diagnostic and therapeutic challenges of drug allergy. Moreover, the paper confirms the role of *in vitro* lymphocyte transformation as a clinically important diagnostic tool in drug allergy.

Case Report

J. B., a 21 year old black secretary, had always enjoyed good health except for possible asthma in childhood and allergies to chocolate and caramel. A month before admission, she was treated with sulfisoxazole (4 grams per day) for vaginitis. Six days before her admission, she developed tender cervical adenopathy and what was interpreted as the symptoms of an upper respiratory tract infection. Aspirin, fluids, and bed rest were prescribed. Three days later she experienced transient chills and fever. The next day she noticed a rash on her forehead which rapidly spread over her entire face. Gantrisin was stopped on this day. On the day before admission, fever and chills recurred. The rash became pustular, and she developed edema of the face and neck. A private physician prescribed benadryl and penicillin, but her symptoms persisted and she was admitted to the George Washington University Hospital.

On physical examination, her temperature was 40.1°C, pulse 100, blood pressure 100/65, and respirations 20 per minute. Her scalp and face were covered with pustules, while her trunk and extremities showed a diffuse maculopapular dermatosis. There was

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marked edema of the face and neck. Tender adenopathy was present in the cervical, axillary, and inguinal areas. The lungs were clear. A grade II/VI systolic ejection murmur was localized to the base of the heart. A tender, smooth liver edge was felt 3 cm below the right costal margin. The spleen tip was not felt. The rest of the examination was unremarkable.

At first it was felt that the patient had a pyogenic dermatitis with a dermatid response. She was treated with two million units of aqueous penicillin IV every six hours. The penicillin was continued for the first three hospital days without improvement in her condition.

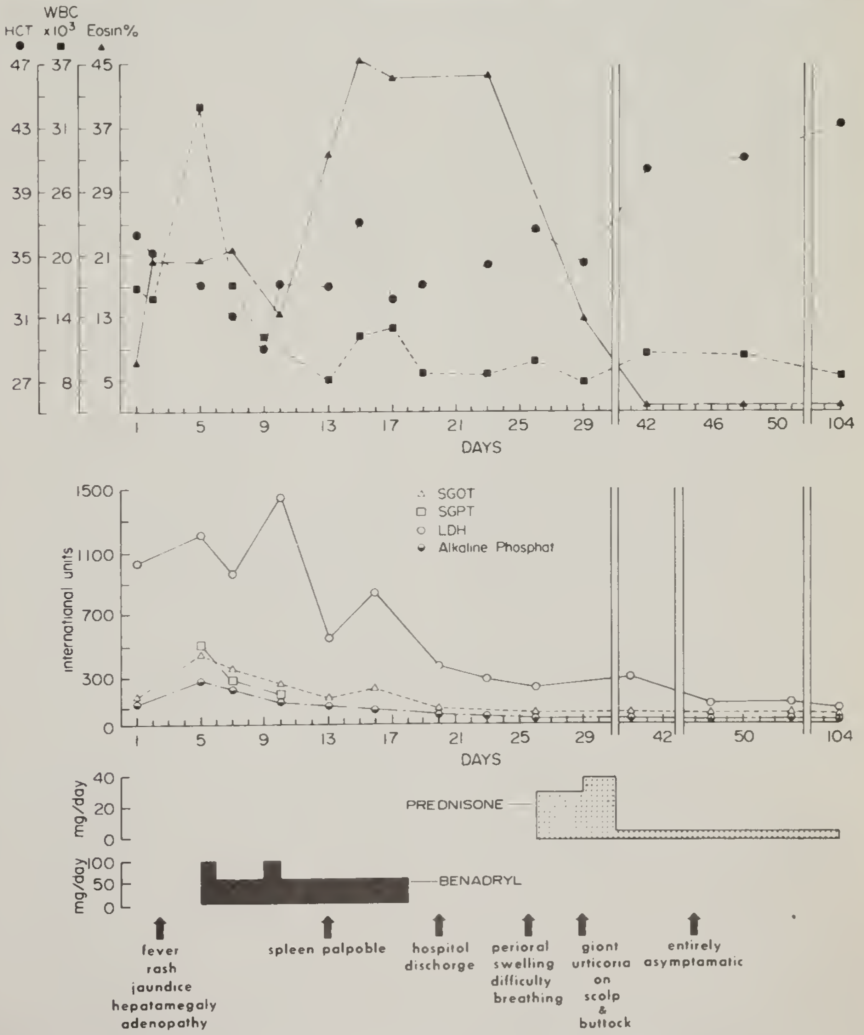
The rash persisted, and the patient complained of severe pruritus which was treated with benadryl 50 mg PO every four hours PRN. By the fourth day, the patient showed no improvement. Temperature spikes as high as 40°C continued. Penicillin was stopped and benadryl continued when it was appreciated that the patient probably had a drug allergy. A bone marrow aspiration done on the sixth hospital day showed eosinophilia, lymphocytosis, and plasmacytosis. A liver biopsy was performed on the eighth hospital day. The needle biopsy of the liver demonstrated focal liver cell necrosis, portal tract infiltration by eosinophiles, lymphocytes, segmented leukocytes and histiocytes, along with foci of endophlebitis. By the eleventh hospital day, the rash was much improved, and the facial and cervical edema were almost completely resolved. On the twelfth hospital day, a hematology consultant reported a palpable spleen. By the fifteenth hospital day, the spleen was easily palpable two to three fingerbreaths below the left costal margin. The patient was discharged on the eighteenth hospital day on no medication, symptom-free, but with the spleen tip still palpable.

Figure 1 shows the pertinent laboratories values during hospitalization and follow-up.

Five days after discharge, J. B. was presented to the emergency room of the hospital complaining of sudden swelling of the lower lip and left cheek, and difficulty swallowing and breathing. She reported the use of an antidandruff shampoo which was found to contain sulfa. She was treated with parenteral antihistamines, epinephrine, and steroids with gradual resolution of symptoms over 12 hours. She was started on prednisone, 40 mg daily. However, three days later, she developed giant urticaria. Her prednisone dose was increased to 60 mg daily, and she was given a single intravenous dose of calcium gluconate.

32 days after initial admission and four days after start of steroid therapy, the liver and spleen were no longer palpable. 101 days after admission, she appeared to be almost completely recovered. Blood count, including eosinophils, and liver chemistries were normal.

Six months after hospital discharge, a study of the *in vitro* response of the patient's peripheral blood lymphocytes was performed. Leukocyte-rich, platelet-depleted plasma was obtained



from the patient six months after hospital discharge by sedimentation and centrifugation as described previously.[4] Mononuclear cells were separated from the leukocyte suspension on Ficoll-hypaque using a modification[5] of Boyum's method.[6] Differential counts on mononuclear suspensions showed greater than 90% lymphocytes, 1% or less polymorphonuclear cells, five to eight percent monocytes. One million lymphocytes were cultured in 20% autologous plasma and 80% TC 199 in three ml cultures and varying concentrations of excipient-free sulfisoxazole (Hoffman La Roche) in duplicate or triplicate. Controls included lymphocytes cultured without sulfisoxazole and lymphocytes cultured with previously ascertained optimum concentration of phytohemagglutinin (PHA, Burroughs Wellcome) of one mcg/ml. PHA cultures contained 500,000 lymphocytes each. The cultures were incubated for four days at 37°C. On the fourth day ^{3}H-thymidine (5000 curies/millimole) was added to the cultures at a concentration of 0.1 microcuries/ml for a three hour period. TCA precipitable was assayed by scintillation counting.

The cells of four individuals were cultured in the above manner (Table 1): patient, J. B., described in this report, H. G. who had never received sulfisoxazole, P. S. and W. M. who had received sulfisoxazole without evidence of allergy two and ten years ago respectively. Only J. B.'s lymphocytes showed increased ^{3}H-thymidine incorporation in response to sulfisoxazole. Decreasing concentrations of the drug were associated with a lowered lymphocyte response. The lymphocytes of all four individuals responded normally to PHA stimulation. The patient's lymphocytes showed no response to penicillin, an additional drug she received during her hospitalization.

Discussion

Drug fever, skin eruptions, hemolytic anemia,[7] agranulocytosis,[8] Stevens-Johnson syndrome,[9,10] temporal arteritis,[11] toxic hepatitis,[12] and myalgia[13] have all been reported as allergic manifestations of sulfonamide sensitization. Of the 151 cases reported in the literature (Table 2), skin eruption appears to be the most common manifestation of sulfonamide allergy. Drug fever is less frequent but is reported in from 25 to 50% of the patients. The incidence of eosinophilia, anemia, and hepatitis vary greatly among the series.

Koch-Weser[14] in a prospective study of 1,361 patients receiving either sulfisoxazole or sulfamethoxazole found that 2.9% had an allergic reaction. There were 29 rashes, 16 drug fevers, 16 incidences of peripheral eosinophilia, two episodes of angioneurotic edema and one each of hemolytic anemia and jaundice.

TABLE 1. Lymphocyte Response to Various Stimulants

	Disintegrations per second			
	J.B.	H.C.	P.S.	W.M.
Sulfisoxazol 200 μgm/ml	479 ± 21	7 ± 3	4 ± 2	4 ± 2
Sulfisoxazol 100 μgm/ml	401 ± 2	9 ± 3	–	–
Sulfisoxazol 50 μgm/ml	323 ± 21	12 ± 8	–	–
Blank	11 ± 2	12 ± 9	22 ± 3	11 ± 5
PHA	5481 ± 249	6462 ± 333	3136 ± 633	2634 ± 1071
100 units Penicillin/ml	22 ± 6	–	–	–

On the other hand, Yow[15] reported no allergic reactions in 1000 patients in whom sulfisoxasole was used at the Jefferson Davis Hospital.

Dujoune[12] reviewed the English language literature and found 107 cases (including their own) of allergic reactions to sulfonamides. Among these were 57 incidences of hepatitis, 25 drug fevers, 22 rashes, and seven episodes of peripheral eosinophilia. Furthermore, 36 of the patients were reported to have had a sensitization period from one to four weeks. In ten cases, toxicity developed after the first exposure to the sulfanomides; while in 19 cases, there was previous exposure before developing toxicity. The total dose administered ranged from one to ninety grams.

Since the case reports after 1950 are more detailed in their clinical and laboratory descriptions, we subjected them to repeated analyses. There were 12 such cases; six[12,16,17,18,19,20] were reviewed previously by Dujoune and the additional six[21,22,10,11,13] (including our own) have appeared in the literature since 1967. There were nine males and three females. Five of the patients were over 50 years of age and seven were less than 50. The ages ranged from 21 to 72. In three, the onset of symptoms began within the first week of sulfonamide therapy. Two of these patients had previously received a sulfonamide. In the remaining nine, symptoms occurred more than one week after start of sulfonamides. Only two of these patients had been previously exposed.

Ten cases were associated with jaundice, hepatomegaly or abnormal liver function tests; eight with fever; eight with rashes; five with peripheral eosinophilia; three with hemolytic anemia; and two with facial edema. When performed, direct and indirect Coombs', LE preps, FANA, heterophile, rheumatoid factor, and serum protein electrophoresis were all within normal limits. Six patients[10,11,16,20,22] were treated with prednisone. There were three relapses[10,20] when the steroid dose was tapered or stopped. Only one drug related death[16] occurred due to hepatic failure.

Zimmerman[23] postulates two mechanisms whereby drugs react idiosyncratically with the host to produce hepatic injury. In one, the responsible drug is assumed to act as a hapten, and subsequently the host mounts an allergic response to the newly formed antigen. In such a reaction, one characteristically sees:

a) a relatively fixed sensitization period of one to four weeks or previous exposure,
b) associated drug fever, rash, and eosinophilia,
c) eosinophilia-rich portal inflammatory infiltration on liver biopsy.

Drugs which produce hepatic injury by this mechanism include the sulfonamides, PAS, chlorpromazine, and the organic arsenicals.

On the other hand, a drug like INH induces liver damage in susceptible individuals in a way that cannot be readily ascribed to hypersensitivity. For example, the jaundice that occurs following this drug is not accompanied by eosinophilia, rash, and fever. Furthermore, the exposure to INH that precedes the jaundice varies from one to over twenty weeks, unlike the one to four week exposure period that precedes the jaundice of the sulfonamides. Zimmerman[23] speculates that an abnormal metabolic degradative pathway could result in the accumulation of hepatotoxic metabolites.

Why does the patient presented in this case report manifest multisystem allergic response to sulfisoxazole, while in others only a rash may occur? It may well be that all patients have some degree of hemolysis and hepatitis, but our laboratory techniques are too insensitive to disclose any but the most intense hypersensitivity reactions. Moreover, Parker[24] postulates that the allergic reaction may be localized to a single organ if an enzymatic or degradative step leading to formation of antigen were largely limited to a single tissue. In this event, the concentration of antigen locally would direct tissue damage to the same area.

TABLE 2. Incidence of Features in Sulfisoxazol Allergy

Series	Cases	Rash	Fever	Eosinophilia	Anemia	Liver Damage
Koch-Weser	38	76%	42%	42%	3%	3%
Dumovne	107	21%	23%	7%	–	53%
Goldsweig	6	67%	50%	33%	33%	50%

Drug allergy is a manifestation of delayed hypersensitivity, which in turn is part of the spectrum of cell mediated immune response. The thymus dependent lymphocyte is known to play a key role in cell mediated immune functions. The evidence,[25,26] which supports the concept of central importance for the lymphocyte, is quite impressive. For example, lymphocytes have been shown to regularly infiltrate the sites of all mediated immune reactions. The capacity to reject allografts and to manifest delayed hypersensitivity reactions are transferable to nonsensitized hosts with living lymphocytes but not with immune serum. Decreasing the number of functional thymus-dependent lymphocytes by neonatal thymectomy, chronic thoracic duct drainage, steroid administration, or specific antisera directed against the lymphocyte increases susceptibility to certain types of infection, prolongs the survival of allografts, depresses the delayed hypersensitivity reaction, and increases vulnerability to the induction of graft versus host reactions.

Antigen stimulation of sensitized lymphocytes in tissue culture has shown that activated lymphocytes synthesize and release cell-free factors which may be the effector molecules of *in vivo* all medicated reactions.[25] These lymphokines, as they are called, include a pyrogenic factor which may be responsible for immune fever; a macrophage inhibitory factor (MIF), which inhibits the movement of macrophages from the reactive site; a mitogenic factor which induces other nonsensitized lymphocytes to divide and form an expanded population of primed antigen-sensitive cells; a cytopathic factor which is toxic for certain target cells; and an inflammatory factor which increases vascular permiability.

Peripheral blood lymphocytes previously sensitized *in vivo* will undergo transformation *in vitro* when incubated with the sensitizing antigen.[27,28] Transformation of lymphocytes, from the peripheral blood of sensitized donors into blast-like cells in the presence of the appropriate drug in tissue culture, has been used as a diagnostic test in hypersensitivity reactions to drugs.[29]

Sulfisoxazole does not stimulate lymphocytes nonspecifically as phytohemagglutinin does, nor does mere exposure to sulfisoxazole sensitize patients, since two individuals exposed to the drug but without allergic reaction failed to show any reactivity when their lymphocytes were incubated with sulfisoxazole. This test confirms the clinical impression of sensitization to sulfisoxazole and is in agreement with previous studies on drug sensitization utilizing this technique.[6,21,22]

The exact etiology of the patient's hemolytic anemia is uncertain. Serial direct and indirect Coombs' test were negative, and spherocytosis was absent in the peripheral blood. Hemoglobin electrophoresis was normal. Glucose 6 phosphate dehydrogenase deficiency is common in the black and has been reported[31] to cause hemolysis in patients receiving sulfonamides. Certainly, hypersplenism may have been the major factor causing hemolysis in this case.

Conclusions

Fever, skin eruptions, and hepatitis are fairly common manifestations of sulfonamide sensitization. Less common are peripheral eosinophilia and hemolytic anemia. Facial and cervical edema are rare but may herald potentially fatal angioneurotic edema.

Patients with previous sulfonamide exposure will usually manifest allergic symptoms within the first week of reexposure; while symptoms in those not previously exposed will be delayed for two to four weeks.

Diagnosis of this syndrome depends on correlation of history and clinical features since no conventional laboratory test is consistently abnormal. Liver biopsy does not confirm the diagnosis since the histology[32,33,34] may be confused with that of viral hepatitis. However, *in vitro* stimulation of a patient's lymphocytes after challenge with one of the sulfonamides appears to absolutely confirm the clinical diagnosis.

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The Influence of Medical School on Selection of Career Specialties

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Introduction

Much concern has recently been expressed about the inadequate supply of primary care physicians in this country.[1,2] In response to these pressures there has been substantial development of programs to train such physician extenders as physician's assistants and nurse practitioners. The number of physician's assistant programs has grown from one in 1967 to over 40 by 1972, while at the same time increasing numbers of nurse practitioner programs are preparing graduates to deliver primary care in a variety of ambulatory settings. Complementing the development of physician extenders has been an effort to produce more primary care physicians. To this end, federal incentives in the form of capitation grants have stimulated the expansion of existing medical schools, and federal and state monies have supported the development of new schools. However, whether an increased number of medical school graduates can be translated into an increased supply of primary care physicians remains unknown, for surprisingly little attention has been paid to the processes whereby medical students select career specialties.

What little is known about selection of medical specialties has been summarized in a recent review by Geertsma and Grinols. The review concentrates mainly on frequency and stability of specialty preferences, and personality characteristics of those choosing the various specialties.[3] Data on patterns of change of specialty preferences during medical school are sparse. It is also unclear to what extent there is a relationship between specialty selection and such commonly used indicators of medical aptitude as scores on medical college admission tests (MCAT) and on the National Board of Medical Examiners (NBME). Yet, if it is desirable to increase the number of primary care physicians, it is important to know what extent the decision to become a primary care physician is already determined at the time of entrance to medical school rather than by actual experiences during medical school.

The purpose of this study is to describe the patterns of change of specialty preferences made at one medical school; to ascertain some of the reasons for change of specialty; and to determine whether the MCAT and NBME scores can be used to predict specialty choices.

Methods

The data were obtained from questionnaires administered to members of the George Washington University School of Medicine class of 1973 at the time of registration their senior year and to members of the class of 1976 at the time of their first year registration. In addition, father's occupation, hometown location, MCAT scores, and scores on Part I NBME, which is given at the end of the second year of medical school, were obtained for members of the class of 1973. Questionnaires given to the senior class asked for specialty preference, if any, during the first year of medical school, and specialty preference at present. Those who had changed specialty preferences were asked to specify time and reasons for change. Members of the class of 1976 were asked for specialty preference, if any, and reasons for selecting that specialty.

Results

Completed questionnaires were received from 99 of 122 members of the fourth year class; 23 students (18.8%) were either not present at registration or did not return the completed form. Questionnaires: 118 of 143 were completed by members of the class of 1976; 25 (17.5%) were not returned.

Specialty preferences during the first and fourth year for members of

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the class of 1973 are shown in Table 1. 28% had not decided on a specialty during the first year, but all had at least a tentative preference by the beginning of the fourth year. Specialties which showed the greatest increase between the first and fourth years were obstetrics-gynecology, the surgical subspecialties, and internal medicine. General surgery and general practice (or family medicine) had an attrition rate of about 25% each.

Table 2 lists fourth year specialty preference according to preference at the time of entering medical school. Internal medicine was the most popular field for students who were previously uncommitted. Those who chose obstetrics-gynecology came from a wide distribution of first year preferences, while those switching to other surgical subspecialties came mainly from general surgery, those who were initially undecided, and internal medicine. Four of the six original psychiatrists had switched to internal medicine by the fourth year, while the other two continued to prefer psychiatry.

Table 3 lists stability of preference between first and fourth year. Of those who had made a first year preference, 52.5% still retained that preference by the fourth year. Stability varied from about 65% for obstetrics-gynecology, internal medicine, pediatrics, and the surgical subspecialties, to 50% for general practice, 40% for general surgery, and 33% for psychiatry.

Mean MCAT and NBME scores according to first and fourth year specialty preference are listed in Table 4. There did not appear to be a great deal of internal correlation between performance on the tests. For example, a different first year specialty group had the highest (psychiatry, general practice, obstetrics-gynecology) and lowest (internal medicine, ob-gyn, surgery) mean scores on the total MCAT, Science MCAT, and NBME respectively. A comparison of the differences in test scores attained by first and fourth year specialty groups permits some estimation of the academic selection process occurring during medical school. Internal medicine was the only specialty which had a rise in all three scores. The greatest decrease occurred among students choosing psychiatry, pediatrics, and general practice. The only statistically significant change was the decrease in NBME scores between first and fourth year psychiatrists ($p < .05$).

Virtually all changes in specialty preferences occurred during the third year of medical school, presumably due to experiences in the principal clinical rotations. Reasons for changing specialties were evenly distributed between positive attraction to the chosen specialty and negative reaction to the abandoned one for all specialties, except internal medicine and obstetrics-gynecology. Five of the 18 students switching to internal medicine did so primarily for academic or intellectual reasons, and all those switching to ob-gyn did so only for positive reasons. Students with physician fathers had a specialty preference stability rate of 54%, essentially the same as for the whole class. There was no obvious influence of geographic origin on type or stability of specialty preference.

Specialty preferences at the time of medical school admission for the class of 1976 are shown in Table 5. Noteworthy is the high percent of students who were undecided (58%), and the large number who chose general or family practice (25.4%). The most frequently stated reasons for selecting family practice were recognition of a need for family practitioners (12 students), humanitarian reasons (10 students), and a desire to practice in a rural setting (6 students).

TABLE 1. Specialty Preferences During First and Fourth Years Class of 1973, George Washington University School of Medicine

	First Year		Fourth Year		
Specialty	No.	%	No.	%	% Change
Undecided	28	28	0		infinite
Internal Medicine	19	19	30	30	+58%
General Surgery	15	15	11	11	−27%
General Practice	12	12	9	9	−25%
Pediatrics	8	8	10	10	+25%
Psychiatry	3	3	13	13	+333%
Obstetrics-Gyn	6	6	6	6	−0−
Other	8	8	20	20	+150%
Orthopedics	2		3		
Ophthalmology	2		3		
Neurosurgery	1		1		
Thoracic Surgery	1		0		
Neurology	1		1		
Pathology	1		3		
Urology	0		3		
Plastic Surgery	0		3		
Emergency Medicine	0		2		
Anesthesiology	0		1		
	99		99		

TABLE 2. Fourth Year Specialty Preference According to First Year Preference, GWU Class of 1973

		Fourth Year Choice						
First Year Choice	Total (First Year)	Internal Medicine	General Surgery	Pediatrics	Ob-Gyn	G.P.	Psychiatry	Other*
Undecided	28	11	3	2	3	2	2	5
Internal Medicine	19	12	1	2	1	–	–	3
General Surgery	15	0	6	0	3	–	–	6
Pediatrics	8	0	1	5	1	–	1	–
General Practice	12	1	0	1	2	6	1	1
Ob-Gyn	3	1	–	–	2	–	–	–
Psychiatry	6	4	–	–	–	–	2	–
Other*	8	1	–	–	1	1	–	5
TOTAL	99	30	11	10	13	9	6	20

* See Table 1.

Discussion

The stability of specialty preferences of the class of 1973 (54%) is similar to that found at Illinois[4] (59%) but greater than Rochester[3] (33%). George Washington students had a higher percentage who were initially undecided (28%) than Illinois (7%); the number of undecideds was not mentioned in the Rochester report. By multiplying the specialty stability rate of 54% by the percentage of students entering medical school with a defined specialty preference (72%), it can be estimated that the specialty selections of 39% of the graduating class of 1973 were determined by the George Washington University Medical School Admissions Committee. Furthermore, even for those who changed specialties there was a tendency to select similar fields; for example, all nine students who left surgery selected either obstetrics or one of the surgical subspecialties.

TABLE 3. Stability of Specialty Preferences Chosen During First Year of Medical School, G.W.U. Class of 1973

		Choice Stable	
Specialty	No.	No.	%
Internal Medicine	19	12	63.2
General Surgery	15	6	40.0
General Practice	12	6	50.0
Pediatrics	8	5	62.5
Psychiatry	6	2	33.3
Ob-Gyn	3	2	66.7
Other*	8	5	62.5
TOTAL	71	38	53.5

* See Table 1.

In contrast to other reports which found psychiatry[5] or surgery[3] to be the most stable specialty preferences, this study showed internal medicine, pediatrics, and obstetrics-gynecology to be the most stable. These discordant results illustrate the difficulty of accurately predicting eventual specialties from the preferences expressed on admission to medical school. Furthermore, achievement scores do not appear to be useful discriminators in helping to predict specialties, although there was a definite trend expressed during medical school toward selection of internal medicine by students with higher scores.

If primary care physicians are defined as general practitioners, pediatricians, and internists, then only 49% of the fourth year class had expressed an interest in primary care. Indeed, 49% is a generous estimate since many internists and some pediatricians are interested only in subspecialty practice or academic medicine[2]; in this study five of the 30 students classified as preferring internal medicine had specified a subspecialty area such as cardiology or pulmonary disease.

While it has been estimated that our present health manpower needs call for a ratio of primary care physicians to specialists of approximately 2:1, current trends in medical career choice run strongly to medical specialization.[6] Over 40% of American graduates in first year resident and fellowship programs in 1968 were in surgical subspecialties. The current deficit of primary care physicians is at present partially compensated by importation of foreign medical graduates and medical subspecialists who practice (reluctantly in some instances) some primary care. Both these solutions appear undesirable. Many of the foreign medical graduates come from countries with greater medical needs and poorer health indices than the United States[7], and active recruitment of these "scarce" physicians to meet our own shortages of primary care physicians

TABLE 4. Mean Achievement Scores According to Specialty Preference, First and Fourth Year, G.W.U. Class of 1973

First Year Specialty	No.	Medical College Admissions Tests (all components)		M.C.A.T. (Science only)		National Boards Part I (Mean)	
Internal Medicine	19	2320		582		516	
Surgery*	21	2272		582		491	
General Practice	12	2420		602		518	
Pediatrics	8	2380		578		512	
Psychiatry	6	2464		598		533	
Ob-Gyn	3	2240		561		560	
Undecided	28	2331		579		518	
TOTAL**	97	2337		584		513	
Fourth Year			Mean Change		Mean Change		Mean Change
Internal Medicine	30	2408	+88	591	+9	529	+13
Surgery*	24	2284	+12	587	+5	483	−8
General Practice	9	2364	−56	591	−11	504	−14
Pediatrics	10	2312	−68	570	−8	509	−3
Psychiatry	6	2400	−64	585	−13	461	−72***
Ob-Gyn	13	2308	+68	593	+32	524	−36
TOTAL**	92	2346	+9	588	+4	510	−3

* Includes surgical subspecialties

** Excludes pathology, neurology, emergency medicine, and anesthesiology

*** $p < .05$

TABLE 5. Specialty Preference on Admission to Medical School, Class of 1976, G.W.U. School of Medicine

Specialty	No.	%
Undecided	68	57.6
General or Family Practice	30	25.4
Internal Medicine	5	4.2
Pediatrics	2	1.7
Psychiatry	2	1.7
Surgery	2	1.7
Ophthalmology	2	1.7
Obstetrics	2	1.7
Community Medicine	1	.8
Tropical Medicine	1	.8
Orthopedic Surgery	1	.8
Radiology	1	.8
Pathology	1	.8
TOTAL	118	99.7

would seem immoral. Utilization of subspecialists as primary care physicians is inefficient in that specific skills and training may not be appropriately used, and contains the potential risk of provider dissatisfaction.

Given the strong current trends toward medical specialization in the face of what some have called a disproportionate number of surgeons in the United States today,[8] one might conclude that increasing the number of medical school graduates will only lead to the production of more subspecialists and that perhaps nurse practitioners and physicians' assistants represent the most logical source of future primary care practitioners. It may be, however, that new pressures, acting either altruistically or through the market place, are already affecting student choice. The large number of undecided students and those choosing general or family practice in the George Washington entering class of 1976 is in marked contrast to the class of 1973. This change does not represent a conscious shift in admission policy, as personnel and procedures have not differed during this period. Although the contrast between the two classes could merely be due to methodological differences, in that the class of 1973 was asked to list first year choices retrospectively and may not have recollected accurately, the distribution of choices listed by the class so closely parallels data obtained from entering medical students at Rochester[3] and Illinois[4] that its validity seems convincing. Although data from one class obviously needs confirmation, the preferences expressed by the class of 1976 differ markedly from previous classes and from recent patterns of George Washington graduates,[9] but confirm general impressions from other medical schools of a recent upsurge in interest in family practice. If the preference stability for family practice is maintained at 50% and if a representative number of the undecided students ultimately choose family practice, we may expect a major increase in the number of family practitioners.

Data from George Washington and other medical schools demonstrate that a substantial degree of specialty choice has already taken place at the time of entrance to medical school and that there are no reliable ways of identifying those students who will change specialties. Nor is it possible to predict eventual choices of those who are initially undecided. If we desire to increase the proportion of primary care physicians, the most effective mechanism may be revision of admissions criteria rather than medical school curriculum changes or such post graduate innovations as family medicine programs.

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For an organization supposedly opposed to change, the AMA has made a lot of changes.

One of the most significant was the addition of an important new voice in the AMA—that of interns and residents. For the first time, these young physicians have not only a voice but also a vote in helping shape AMA policies.

Recently, the AMA House provided the same opportunities for membership and participation to medical students.

That's not all. In another important change, the AMA's council-committee structure has been streamlined. Some councils and committees have been dropped. Others have been made more efficient by reducing their size to seven members for councils and five for committees. And to permit more frequent infusion of new members and ideas, maximum tenure of service has been reduced to seven and five years, respectively.

The AMA *has* made a lot of changes. Changes to make it more responsive to the ideas of *all* physicians . . . changes to make it more effectively serve the needs of the profession.

Change will continue. But it will be decided only by those of you interested and dedicated enough to be a force in that change.

Join us.
We can do much more together.
American Medical Association
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From the Editors

In assuming the editorship of the *Annals* from Doctor Wallace Yater, on the first of this year, we also assumed a debt of gratitude. Doctor Yater, in his long years as Editor, created and maintained a scientific journal which is now our responsibility to perpetuate.

In defining our aims and philosophies as we begin this new task, the first question is why do we need an *Annals* at all? Standard responses are that a medical society journal offers prestige, or that "everybody has one," or that it is a vehicle for papers from the membership. These arguments are valid, at least in part, but we believe that the primary value of a journal is to record and collect data for the medical scientific world.

In addition to these objectives, we further believe that we must give priority to scientific papers that offer material not documented elsewhere, or that is unusual enough to warrant cataloging. We share the hunger of all editors for excellence in papers (and get a surprising number of good ones). Our inclination is to select papers of wider general interest and more clinical orientation. There is some reluctance to accept very technical papers or those of interest to a small readership.

While the scientific papers are the meat of a medical journal, there should be other courses, too. Special articles and series and non-medical papers of particular interest are to be very much a part of the Annals, with an increasing emphasis on medical editorials of timely importance.

However, two major limits face us continually: lag time (not just the mechanics of publication, but time to have papers reviewed, or revised, or solicited), and space limitations (a function of cost). The latter makes it mandatory though unfortunate that we reject some papers that are good enough to publish. The lag time in publication is no news to the reader of any journal. However, in this Society, dissemination of timely information has been accomplished by the increasing activity and importance of the Newsletter.

Finally, there are two primary sources of papers, manuscripts spontaneously submitted and those solicited for issues dedicated to specific hospitals. With this issue, we present a full set of instructions for the preparation of manuscripts for THE ANNALS; please notice we now require the submission of abstracts. We are grateful to our authors and to the men who have collected the manuscripts for the hospital numbers: Dr. Jay Shapiro (Washington Hospital Center), Dr. Philip Cox (Cafritz Hospital), Dr. Karl Jonas (Doctors Hospital). They have done this during this past year without the recognition that they deserve, but which is now extended.

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Information to Authors of Manuscripts Submitted to The Medical Annals of the District of Columbia

The following suggestions constitute a guide to authors who submit material to the ANNALS. Many of the suggestions are from the AMA "Suggestions to Authors" with ANNALS additions and revisions.

The MEDICAL ANNALS OF THE DISTRICT OF COLUMBIA is published monthly by the Medical Society of the District of Columbia for the promulgation of information of scientific, general medical and personal interest. All articles and correspondence should be sent to the Editorial Offices, Medical Annals of the District of Columbia, 2007 Eye Street, N.W., Washington, D.C. 20006.

EXCLUSIVE PUBLICATION: Articles are accepted for publication on condition that they are contributed solely to this journal.

MANUSCRIPT

The entire manuscript, including footnotes and case reports, should be submitted unrolled, with double type spacing. An original copy and one carbon copy should be submitted, and a carbon copy should be retained by the author.

The title should not exceed 80 characters and spaces. If a subtitle is used, it should not be connected grammatically to the main title.

The by-line, the author's given name and initial or given name alone should be supplied. The M.D. degree or highest academic degree should be listed for each author. Not more than six names should be included as authors, unless the communication is the report of a committee.

The footnotes, hospital or university affiliation when study was done, should be listed. Present affiliation and location (if different from that at time of study) should be given. Acknowledgements should be limited to persons, foundations, agencies or companies supplying drugs, funds or apparatus free of charge or otherwise making an extensive contribution to the study.

REFERENCES

The number of references should not exceed 18 single complete bibliographic citations, except in Special Articles.

References should be double spaced, on a separate sheet, and listed in order of citation in the text. Superior numbers should be inserted in the text at points of citation.

References should be given in the style regularly used in THE ANNALS, eg:

> Seremetis, M. G., DeGuzman, V. C., Lyons, W. S., Peabody, J. W.: Complications of Cardiac Pacemakers, Medical Annals of D.C., 1973, 42, 165.

TEXT

Use generic or descriptive names of drugs when available. Trade names, capitalized, may be given in parentheses when the drug is first mentioned.

Statistics should be checked for consistency within the text and for agreement with graphs or tables.

Laboratory data should not be given in abbreviated form but in full (e.g., "hemoglobin level, 12 Gm. per 100 ml." rather than "Hb. 12 Gm.%").

Figures should be used for number 10 and above, laboratory measurements, percentages, and ages.

Metric equivalents should be given for dosage and body height and weight.

Centigrade equivalents should be given for Fahrenheit body temperatures, and vice versa.

Abbreviations should be used sparingly, with expansion given for those not listed in standard medical dictionaries.

The meaning of "we" should be clarified, especially if there is only one author. Avoid use of editorial "we."

SUBHEADINGS

One center heading should be supplied for about every three pages of double-spaced text copy. Subdivisions of main topics should be indicated by side headings.

SUMMARY

The summary should be brief, giving specific facts concerning the study and its results.

ADDRESS

The street address of one author should be given at the end of the article for reprint requests and correspondence.

TABLES

The title should be given at top of the page for each table.

Approximate placing of tables in text should be indicated, and each table should be referred to in the text.

The meaning of abbreviations should be clear, with those not listed in standard medical dictionaries expanded in a footnote to the table.

There should be no discrepancies in the totals.

Figures should be consistent with the text, without extensive duplication between tables and text or graphs.

All material under each column heading should be parallel in meaning.

Data should be listed in vertical rather than horizontal columns.

Simple tabular material should be incorporated into the text in sentence form.

ILLUSTRATIONS

Only necessary illustrations should be submitted.

Photographs should be submitted as unmounted black-and-white glossy prints.

Graphs and line drawings should be prepared with black india ink on white paper, with uniform lettering which will be legible when the illustration is reduced to 3-1/8 in. in width.

Lettering on a figure should be checked for correct spelling and style consistent with the manuscript.

The top of each illustration should be indicated.

Permission should be received and credit given in legend or footnote for use of illustrations published elsewhere.

Permission should be received from patients for use of pictures of themselves. Eyes of patients should be blocked out.

Arrows should be inserted to pinpoint lesion or any important feature.

Do not attach paper clips or cellophane tape to photographs.

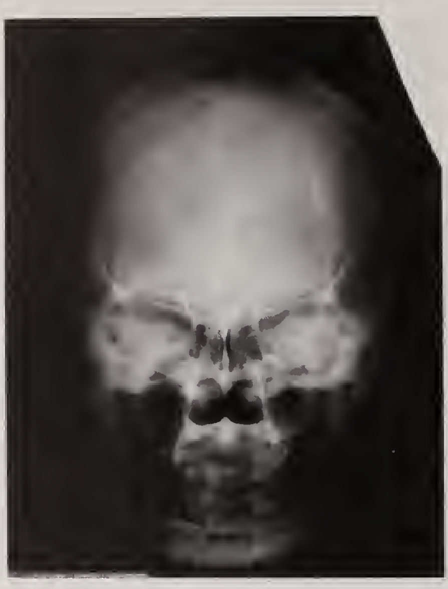
SYNOPSIS-ABSTRACT

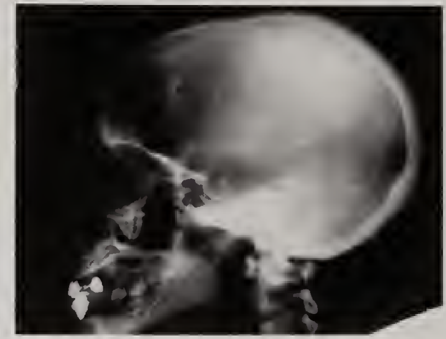
A synopsis-abstract not to exceed 150 words must accompany the manuscript.

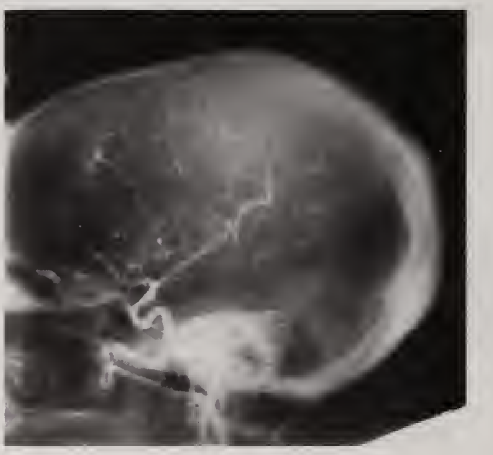
THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center

A 42 year old housewife is brought to the ER with a laceration over the left frontal area following a car accident. She was alert and there was no neurological deficit.







DIAGNOSIS: Meningioma, Left Frontal Convexity

Note in the skull radiographs (Fig. 1 and 2) the hyperostosis in the frontal region and especially in the lateral projection the prominence of vascular channels. (Middle meningeal artery)

Note in Fig. 3, a lateral projection of a common carotid angiogram, the prominent middle meningeal artery coursing towards and entering the center of the lesion. The meningioma was successfully removed.

Meningiomas arise from arachnoid villi and, therefore, are most frequent in the parasagittal region. Their peak incidence is in the 4th-5th decade of life and they compress the surrounding brain usually without invasion.

It is said that in 40-45% of cases the plain radiographs show changes suggesting the diagnosis, namely:

1. Hyperostosis which occurs in roughly 20%
2. Prominence of vascular channels in approximately 20%
3. Calcification in the tumor in roughly 10%

Nonspecific changes such as pineal shift and pressure changes in the sella, of course, also occur.

In over 90% the lesion has a high affinity for injected radioisotopes–a positive brain scan.

Meningiomas in general have a "double blood supply," i.e., they are supplied by branches from the external carotid artery (middle meningeal artery) and branches from the internal carotid.

Edited by Gunther J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

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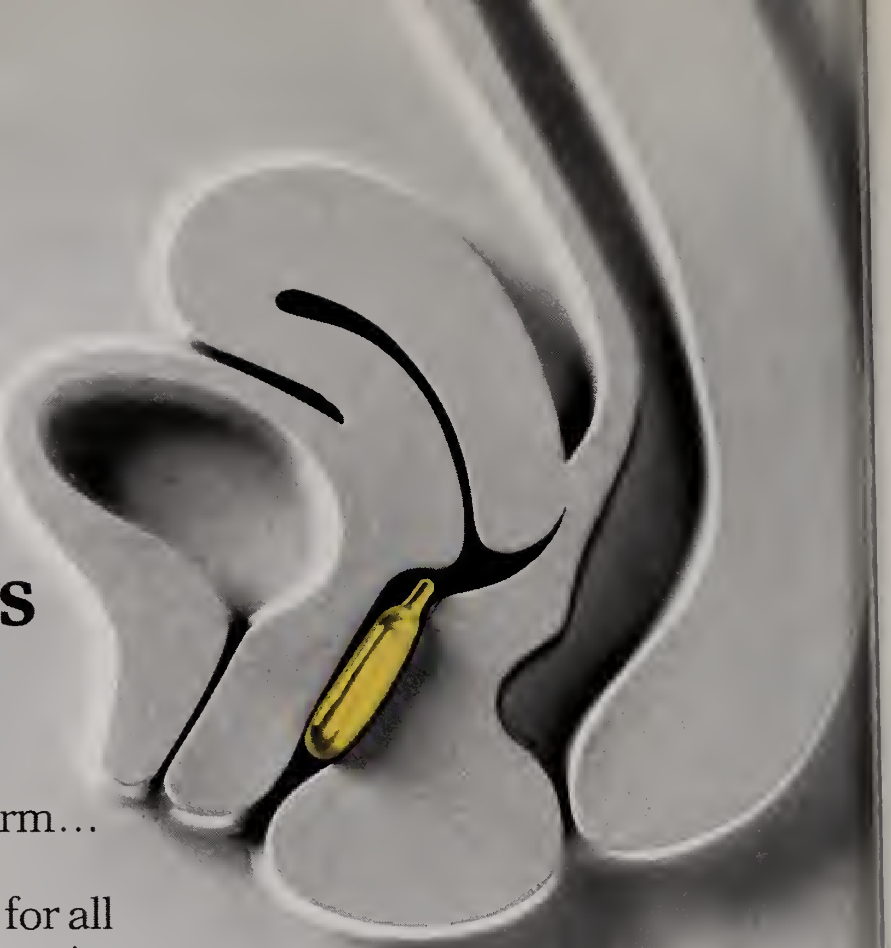

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Adverse Reaction: Clinical reports of sensitization or temporary irritation with CANDEPTIN Vaginal Ointment, Vaginal Tablets or VAGELETTES Vaginal Capsules have been extremely rare.

Dosage: One vaginal applicatorful of CANDEPTIN Ointment or one Vaginal Tablet or one VAGELETTES Vaginal Capsule is inserted high in the vagina twice a day, in the morning and at bedtime, for 14 days. Treatment may be repeated if symptoms persist or reappear.

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Store under refrigeration to insure full potency.

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References: 1. Olsen, J.R.: Journal-Lancet *85* 287 (July) 1965. **2.** Giorlando, S.W.: Ob/Gyn Dig. *13* 32 (Sept.) 1971. **3.** Decker, A . Case Reports on File, Medical Department, Julius Schmid. **4.** Giorlando, S.W., Torres, J.F., and Muscillo, G.: Am. J. Obst. & Gynec. *90*: 370 (Oct. 1) 1964. **5.** Lechevalier, H.: Antibiotics Annual 1959-1960. New York, Antibiotica Inc., 1960. pp. 614-618. **6.** Friedel, H.J.: Maryland M.J., *15*:36 (Feb.) 1966.

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STEPHAN NEWMAN, M.D. Office: 10401 Old Georgetown Road, Bethesda, Maryland. Born in Washington, D.C. Medical degree: Georgetown University, 1966. Specialty: Oncology–Internal Medicine.

FRANKLIN PEPPER, M.D. Office: 4600 Duke Street, Alexandria, Virginia. Born in Omaha, Nebraska. Medical degree: University of Nebraska, 1965. Specialty: Psychiatry.

RITA RIGOR, M.D. Office: None yet–lives in Maryland. Born in Manila, Phillipines. Medical degree: University of Santo Tomas–Phillipines, 1965. Specialty: Obstetrics-Gynecology.

Changes in Membership

Transfers

Active to Associate: Daniel Prieto, M.D., In Bae Yoon, M.D.

Associate to Active: Jon Gulbransen, M.D., Ruth Jacoby, M.D., Gerald Schuster, M.D., Harry C. Stein, M.D., Henry Capozella, M.D.

Resident-Intern to Active: Lillian Beard, M.D., Hugo Ceasar, M.D., Edward J. Taylor, M.D.

Active to Special: Catherine Knop, M.D., Theodore Winship, M.D.

Reinstatements

Associate: Joseph A. Dugan, M.D., William Driebe, M.D.

Resignations

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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For many overweight persons the answer is not a "crash" program but a "crack-down" on the quantity and quality of food eaten. Sound advice for dieters remains: Follow a good, balanced diet and wage war against bad eating habits. To lose weight, eat less.

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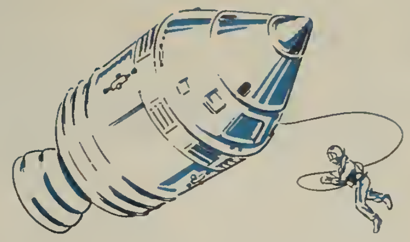

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Howard E. Ticktin
1927–1973

Dr. Howard E. Ticktin, noted liver specialist and associate clinical professor at George Washington University, died April 2, 1973 of an apparent heart attack while on vacation in Rome. He resided at 6500 Bradley Blvd., Bethesda, Md.

Born in Cleveland, Ohio, he received his B.A. degree from George Washington University, Washington, D.C. and his M.D. degree "with distinction" from George Washington University's School of Medicine.

He interned at George Washington University Hospital and served residencies at the D.C. General Hospital, the George Washington University Hospital in Washington, D.C. and the Peter Bent Brigham Hospital in Boston, Mass.

From 1946-1947, Dr. Ticktin served as a private in the Medical Detachment of the Army Service unit of the U.S. Army.

Dr. Ticktin was a research associate at D.C. General Hospital in the cerebral metabolic laboratory and chief of George Washington University's medical service division for 12 years, as well as former associate director of the medical school's division of gastroenterology. He was a consultant in liver diseases for Washington Hospital Center, Bethesda Naval Hospital, St. Elizabeths Hospital and the White House. He was also president of the Metropolitan Medical Center here.

In 1962-1963, he headed the George Washington University Medical Alumni Association and in 1965-1967 was chairman of the Association's Alumni Giving Program which helped finance new medical school facilities.

Dr. Ticktin was also chairman of three American Gastroenterological Association committees, and led a successful effort to increase training programs for gastroenterologists.

He worked as a consultant to the Food and Drug Administration, Wyeth Laboratories, and various hospitals; was an editor of Enzymologia Biologica et Clinica; and was recently named director of the area's Blue Shield medical payment program.

Much of Dr. Ticktin's recent time was spent heading a group of physicians who wanted to build a new hospital in Northwest Washington.

He was a member of the American Medical Association, the American Heart Association, the Washington Heart Association (scientific council), the American Federation for Clinical Research, the American Gastroenterology Association, the American Association for the Study of Liver Diseases, the New York Academy of Sciences, the American College of Physicians, and the American Board of Internal Medicine.

In addition, Dr. Ticktin was a 14 year Active member of the Medical Society of the District of Columbia as well as chairman of the Society's Fee Committee for 1973.

He is survived by his wife, Janet, of the home; three children, Nancy B. Ticktin, John A. and Richard D. Ticktin, all of the home address; and his mother, Mrs. Mae Ticktin of Miami Beach, Florida.

Elisabeth K. Kalandros, M.D.
1919–1972

Dr. Elisabeth K. Kalandros, an anethesiologist who practiced in the Washington area, died June 7, 1972. She resided at 11309 Willowsbottom Drive, Columbia, Maryland.

Born in Vienna, Austria, she received both her undergraduate degree and her M.D. degree from the University of Vienna. She served internships in the Krakenhaus Lainz Hospital, Vienna, and the University of Vienna and served residencies in the University of Maryland Hospital, Baltimore, the Emergency Hospital, Washington, D.C., and the Washington Hospital Center. She also taught at the University of Vienna in the Biochemistry Department.

Dr. Kalandros was an associate member of the Medical Society of the District of Columbia for four years and an active member of the Society for eight years. During her membership with the Society, she served on the Maternal Welfare Committee and the Emergency Medical Service Committee.

She is survived by her husband, Basil, and a daughter, E. Susanna Doringer.

Charles K. Holmes, M.D.
1891–1973

Dr. Charles K. Holmes, Washington-area physician and surgeon, died on April 5, 1973. He resided at 6205 Kennedy Drive, N.W., Washington, D.C.

Born in St. Paul, Minn., he received a Ph.B. degree from Hamline University in St. Paul, and his M.D. degree from the University of Minnesota, Minneapolis, Minn. He served his internship at the Bismarck Clinic in Bismarck, North Dakota and three separate residencies in the U.S. Army (1917-1919, 1941-1946, and 1948-1952). His early positions with the army included the post of Commanding Officer, Med Tech School, Army & Navy Hospital, Hot Springs, Arkansas, and service with the U.S. Control Group, London, Public Health Occupation of Germany. During his later years with the armed services, Dr. Holmes was with the Office of the Surgeon General as Colonel, MC, Executive, Civilian Component Activities. He also served on the staffs of Asbury Hospital, Minneapolis, and St. Mary's Hospital, Minneapolis; as Assistant Instructor of the University of Minnesota's Outpatient Clinic; and as the sole medical consultant for the National Association of Letter Carriers Health Benefit Plan in Washington.

Dr. Holmes was a member of the American Medical Association, the Hennepin City Medical Society and an Associate Member of the Medical Society of the District of Columbia for 24 years.

He is survived by his wife Mabel Jane, of the home; his son, Charles K. Holmes, Jr., of Atlanta, Ga., his brother, Dr. Frank O. Holmes of Boston, Mass., and three grandchildren.

Norman D. Comeau
1921–1973

Dr. Norman D. Comeau, Mt. Rainier, Maryland internist and former chief of staff at Prince Georges General Hospital, died May 14, 1973. He resided at 3221 Kempton Road, Martin's Woods, Maryland.

Born in Spencer, Massachusetts, he received an AB degree from Clark University in Worcester, Massachusetts and an M.D. degree from Boston University School of Medicine, Boston, Massachusetts. He served his internship at Boston University Service, Boston City Hospital and his residency at Georgetown University Hospital. He was an instructor in internal medicine at Georgetown University Hospital, D.C. General Hospital and Prince Georges General Hospital. He was Chief of Staff of Prince Georges General Hospital from 1960-1961, when he became Chief of the Internal Medicine Department, and was a staff member of Georgetown University Hospital. In addition, he was associated with Sibley Hospital and Garfield Hospital and was a courtesy member of the staff of D.C. General Hospital.

During the war, Dr. Comeau was a lieutenant, junior grade with the Navy Reserve (active) and served as senior ward medical officer at the U.S. Naval Hospital in Newport, Rhode Island and Senior Medical Officer of Destroyer Division 122.

Dr. Comeau was an Associate member of the Medical Society of the District of Columbia for 20 years. He was also past president of the Prince Georges County Medical Society and a member of the Advisory Board, Mental Health Clinic, University of Maryland, the Medical and Chirurgical Faculty of the State of Maryland and a member of the Military Surgeons.

He is survived by his wife Judy and son, Perry Anthony, of the home; and a brother, Lionel, of Worcester, Massachusetts.

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book REVIEWS

Pathogenic Mycoplasmas—A CIBA FOUNDATION SYMPOSIUM. Price, $18.75. Pp. 404 with illustrations. New York: American Elsevier Co., 1972.

The growing interest in mycoplasma has indicated the need for a comprehensive reference on the subject. The CIBA Foundation Symposium on Pathogenic Mycoplasmas supplies this need. The title is somewhat misleading because of greater emphasis on morphology, cytology, isolation, growth, identification and immunochemistry than on pathogenesis, but these former considerations are the most important for those unfamiliar with the area. The monograph deals with a comprehensive discussion of the relationship of mycoplasma to plant, insect and animal life and emphasizes the magnitude of the known and unknown biologic significance of these microbial forms.

In the discussion of pathogenesis much emphasis was directed to the fulfillment of Koch's postulates. There was no consideration of mycoplasma pathogenesis in rheumatic diseases, for example, which may require presensitization of the host by mycoplasma antigen prior to final antigenic challenge with the precipitation of the disease state. Perhaps the time is at hand to re-examine such long established biological laws in the framework of pathogenesis predicated on host parasite interaction.

The most informative section in the book deals with immunology and immunochemistry of mycoplasma. Much of the discussion is, however, primarily academic. An opportunity was missed to dwell on mycoplasma pneumoniae with its proven identity as the Eaton agent in the pathogenesis of a major type of virus pneumonia and to update infectivity versus immunity in this area. Another area of pathogenesis which was incompletely covered was in relation to mycoplasma and their production of diseases in swine and fowl. This area has received a great deal of attention in recent years and may serve as an important basis for comparative studies on humans.

In conclusion, despite certain weaknesses, this monograph on pathogenic mycoplasma is must reading for physicians who feel the need to become more thoroughly acquainted with this relatively new area of disease pathogenesis.

THOMAS MCPHERSON BROWN, M.D.

Clinical Nephrology. SOLOMON PAPPER. Little, Brown and Company, Boston, 1971, 539 pages.

This is a book for the non-nephrologist although there are parts that are an excellent review even for the specialist in renal diseases. The emphasis is on clinical medicine and for that reason the author does not go into the detailed and often boring presentation of pathology, structure, and function of the kidney. There is enough for review but not so much to make the reader lose interest. Most of the diseases of the kidney are covered although some are too brief to be of much value, such as polycystic disease. The chapters on the evaluation of the patient, acute and chronic renal failure are particularly good. The handbook section is somewhat of a disappointment but it does contain practical information such as test and diet information that are difficult to find elsewhere. It is a book for the internist, house officer and student or anyone who wants a quick, easy-to-read reference.

ALVIN E. PARRISH, M.D.

Cardiac Hypertrophy. NORMAN R. ALPERT, Editor. Price, $25.00. Pp. 641 with illustrations. New York: Academic Press, 1971.

This monograph is concerned with the many aspects involved in understanding cardiac hypertrophy. It is not an esoteric treatise of interest to only a few scientists. Rather, it is a prodigious and profound presentation that clarifies and distinguishes cardiac growth from that of other organs. Cardiac hypertrophy provides a forum for the basic science and clinical medicine.

Original investigations, by 87 contributors renowned in the field, reveal the myriad phenomena involved in cardiac hypertrophy. Current concepts and recent advances comprise forty-eight chapters. Diverse disciplines of science expound the thesis that cardiac hypertrophy is the heart's expression of and to an adaptive mechanism of increased work-load. Initial chapters focus, teleologically, on the unique character of the heart.

At birth the number of muscle fibers is equal in both ventricles. Almost with the first natal breath and consequent closure of the ductus arteriosus, disparity in ventricular size is manifest due to altered ventricular function and responsibility. Thus, inequality of ventricular muscle mass is not predetermined genetically. Ventricular hypertrophy is achieved not by cellular hyperplasia but through the increased number of intra-cellular organelles. Sarcomere length is not changed; constituent myofibrils increase only through an increase of myofilaments. Myosin, mitochondria, sarcoplasmic reticulum resort to molecular turnover to renew intra-cellular integrity and function.

Cardiac growth is not unrestricted. It is influenced by many factors: protein metabolism and turnover of RNA and DNA, blood supply and hormonal milieu. Increase in DNA in the mature animal may be due to a proliferation of interstitial cells and other nonmuscular and non-contractile elements.

The interface where normal cardiac growth becomes abnormal ventricular hypertrophy is often indiscernible. Mechanical and energy characteristics may seem unchanged. However, whether as an isolated muscle strip or as a total functioning unit scrutinized in the physiological or chemical laboratory, both animal and human myocardium reflect altered correlates of energetics and mechanical efficiency. Sub-clinical and overt evidence of heightened end-diastolic ventricular pressure and volume and decreased ventricular ejection faction may represent sustained effects of increased work loads. Likewise, clinically, the border between the normal and the failing heart is subtle and often difficult to recognize.

Reluctance to accept the conclusions of the experimental laboratory, where these correlates are artificially and acutely induced, is understandable. Such findings may be regarded as invalid comparisons to myocardial hypertrophy in man. However, physiologic observations in man in the cardiac laboratory support the concept that ventricular hypertrophy in man, as well as in the animal, is an adaptive mechanism and the consequence of increased work.

Finally, the electrical correlates of the hypertrophied heart are presented in the concluding chapter. An introduction to "advanced" electrocardiography, the electrical field surrounding the hypertrophied right ventricle, body surface potentials, multiple di-pole and multi-pole approach to electrocardiography reflect the variegated disciplines and potentials that were mobilized to extract the maximum information and clearest possible understanding of the biologic dynamics that participate in ventricular hypertrophy.

In any multi-authored text, repitition is unavoidable. Here and there, an occasional chapter is all too brief and seems a mere editorial. These are minor criticisms.

In this monograph, Editor Platt and his prestigious participants provide the physician and investigator with an abundant volume of information. "Cardiac Hypertrophy" deserves a place on the shelf of every medical library.

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index of advertisers

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Ralph W. Lee & Company T-359
McDermott Insurance, Inc. C2
Mutual of Omaha C3
Russell, Marsh & Kennedy 13

Investment Planning
Suter Associates Retirement Planning Company T-355

Nurse Registries
Association of Undergraduate and Practical Nurse Registry T-366
District of Columbia Manpower Administration T-368

Nutrition Education
Dairy Council of Greater Metropolitan Washington, D.C. T-362

Pharmaceuticals
Burroughs Wellcome & Company T-351
Geigy Pharmaceuticals 12
Eli Lilly & Company 10
McNeil Laboratories, Inc. 6
Pharmaceutical Manufacturers Association 4–5
William P. Poythress & Company . . T-363, 364
Roche Laboratories . . 2–3, 8–9, T-360–361, C4
Julius Schmid, Inc. 000
G. D. Searle & Company T-352–353
Smith, Kline & French Laboratories T-354
The Upjohn Company 11

Pharmacy
Peoples Drug Stores T-346

Real Estate
Anderson-Stokes, Inc. 7
Shannon & Luchs T-358

Services
Business Communications Company T-359

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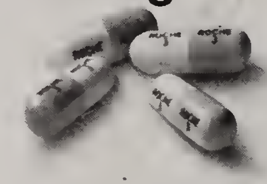

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President's Message 1
The Rx. Irving Burka, M.D.

Editorials 2
Psychiatry: Art and Business. William G. Tompkins, M.D.

An Alternate Method of Treating Chronic Fissures-In-Ano. John J. O'Connor, M.D.

SCIENTIFIC ARTICLES

The American Connection: Handguns and Homicide. Stefan A. Pasternack, M.D. 369
Discussion by Paul Chodoff, M.D. 374

Giardiasis in Young Adults. Jane Henkel Chretien, M.D., John G. Eswein, M.D., Vincent F. Garagusi, M.D. 375

An Epidemiologic Study of Gonorrhea and Cancer of the Prostate Gland. M. Y. Heshmat, M.D., DR.P.H., J. Herson, Ph.D., J. Kovi, M.D. and R. Niles, A.B. 378

Psychological Problems in the Care of the Institutionalized Aged: A Look at D.C. Village. Paul R. Robbins, Ph.D., Jack Kleh, M.D. and Herman A. Meyersburg, M.D. 385

A Case of Severe Varicella in an Adult. Habib O. Farhoudi, M.D., Vinod R. Mody, M.B.B.S., F.R.C.P.E. and D.T.M. & H. and Corolynne G. Branson, M.D. 390

OTHER FEATURES

ECG Problems 384

The View Box 396

New Members 407

Obituaries 411

(continued)

Book Reviews 409
Pathophysiology of Gestation. (Assali and Brinkman) Reviewed by Milton W. Werthmann, Jr., M.D.

Justifying Violence. (Blumenthal, Kahn, Andrews and Head) Reviewed by Edward I. Kushner, M.D.

Functional Aids for the Multiply Handicapped. (Robinault) Reviewed by Margaret Kenrick, M.D.

Information for Authors 416

Advertising and Subscription Information 8

Index to Advertisers 9

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PRESIDENT'S MESSAGE

The Rx

Irving Burka, M.D.

There recently came across my desk an announcement from the Pharmaceutical Association of the District of Columbia stating that, henceforth, its members, for their protection, would begin monitoring physicians' prescriptions for certain drugs, and as a consequence would limit or discontinue dispensing such drugs as they deem to be deleterious to the community. Simultaneously I received communication from several physicians informing me and complaining that patients with intractable pain due to malignant neoplasms were having difficulty having prescriptions filled for dilaudid.

With increasing frequency another precinct is being heard from. This is the strident pontifical voice of the F.D.A. as to, "Thou shall" and "thou shall not." This voice is often first "heard" in the media, with the resulting implication that the practitioners are inept while the Great Father, the F.D.A., knows best. In this propagandizing, there is unquestionable implication that our prescription writing habits and usage are being manipulated by strings from the Pharmaceutical manufacturers. Furthermore every day articles appear in the daily press, magazines, journals, etc. as to the specific "drug of the day" being abused. If it isn't Methadone, it is Amphetamine, Barbiturates, tranquilizers, etc. Of course, we must not forget the daily warnings against all and sundry possible carcinogenic chemicals which flood the air waves and the written page.

In all of this I see a trend to circumscribe, diminish and eventually to emasculate the physician in his ability to treat his patients, as well as curtailing the rights of the patient.

It is one thing to protect the public against harmful or impure drugs, or in instances where a drug such as thalidomide is found to be dangerous, but it is quite another matter where patients in dire need of pain relievers must go from drug store to drug store seeking one that will fill such a prescription and being rejected for the reasons outlined above.

The physician, who certainly knows his patient best, has the responsibility and obligation to prescribe what he feels best, and should be allowed to do so as long as that privilege is in conformity with the rules of good practice, common usage, and legal obligation.

It isn't the F.D.A. that has the responsibility for the patient care. As I see it, its province lies in the field of education and control, but not in the practice of medicine. Our pharmaceutical colleagues who have shared with us for many years the responsibility for drug dispensing must remain in that role. They should be partners, but not the sole arbitrator of what shall be dispensed and what shall not.

It should be the prerogative of the physician to prescribe for his patient what he deems to be honestly necessary for his (the patient's) welfare. The pharmacist's responsibility should be to dispense medication in response to a legal prescription. The F.D.A. should keep the doctor informed as to the compatibility, toxicity and effectiveness of therapeutic drugs.

EdiTORIAlS

PSYCHIATRY: ART AND BUSINESS

Recent changes in the legislation concerning the subsidation of training programs in psychiatry have markedly reduced or eliminated funding for training of physicians in the art and practice of psychiatry. The folly of the pen has been the poison of many medical school psychiatric training programs through out the nation. Directors and staffs of training institutions have worked 24 hours a day, rustled with anxious thoughts and decisions, and sweated through compromises with the idealistic form and plan for training, finally to emerge with a reality that the art and practice of psychiatry is indeed part and parcel of the business of the practice of psychiatry.

These facts are well demonstrated by the recent changes announced by the Department of Psychiatry of the George Washington University Medical Center at a recent staff meeting. It was learned that the full time academic staff will have the responsibility for producing and providing a large percentage of the income for training of the psychiatric residents while at the same time providing its usual high level of competency and expertise in the training area. The full time staff must utilize many of the in-patient beds for income production as well as for teaching purposes. Referrals of patients completing their hospitalization will probably be made to the same physicians for continued treatment on an out-patient basis within the clinical facilities of the University Medical Center. This is indeed an emerging role of a medical training program and it is causing the emergence of a host of various feelings amongst the full time academic staff, the attending physicians and the ward personnel. The full time academicians have to get the business. The attending psychiatrists, members of the staff will have to get their business elsewhere. About 67% of the bed capacity of George Washington's in-patient unit on psychiatry will be under the control of the full time staff, leaving 33% of the in-patient beds for all of the attending psychiatrists who care to use the facilities of the psychiatric unit. Although the handwriting has been on the wall for the past year, the tickle of the feather is no less painful to the attending physicians who are responding with outbursts of feelings leading all the way to rage. The corporate structure has flexed its muscles to such an extent that the individual practitioner is screaming, "Where is the live and let live concept?" There are extremely important considerations to both sides of the question as to who has the controls of the use of the in-patient beds. The attending psychiatrists are reeling and running to join the staffs of other hospitals in hopes that they may have other outlets to hospitalize their patients who may need services of this type in the future. Proclamations of a complete wipe-out of in-patient facilities which in the near future are not only defensive but may be in reality orientation. The attending physicians are finding it difficult to rationalize their need to continue supervising residents, students and staff and satisfying their own needs to keep in contact with academic medicine when there is no business for them. They envision quite a scramble and fight for the small number of beds available to them. We certainly expect to see many more private day treatment centers arising in the metropolitan area for the treatment of the psychiatric patient. Several models of day treatment facilities are viable and provide an alternative to hospitalization. The Potomac Foundation, the Silver Spring Day Treatment Center, the P. I. Day Treatment

Center in Kensington, Maryland, as well as the day treatment facilities of many of the general hospitals through out Maryland and D. C., provide an interesting change in the direction of services which can be provided for the psychiatric patient who requires more than out-patient, office therapy.

The new corporate structure of the George Washington University training and service center represents an emerging model of practice of psychiatry in the nation. Without a doubt and without this model, the training centers of psychiatry can not survive. The task of maintaining an expert training program while providing excellent service to the patient is probably more difficult than the singular function of training physicians in psychiatry as represented by the previous models. The dual responsibility of providing excellent training and making money is not an easy combination to wed.

Changes in funding for health care and proposed changes in legislation for funding of health in the United States will cause many more problems for both the University based training centers as well as the practitioners in the private sector. We can not afford to maintain the polarized position of antagonism toward the changes that are necessary by the University medical services. Both sides must find ways of bridging the gaps that have occurred so that a unified, cooperative, understanding and free exchange of communication exists and that the art of the practice of psychiatry will never become subservient to the business of the practice of medicine and psychiatry.

WILLIAM G. TOMPKINS, M.D.

AN ALTERNATE METHOD OF TREATING CHRONIC FISSURES-IN-ANO

In 1968 Lord introduced a new approach to hemorrhoidal disease, based upon forceful anal dilatation. Since that time further experience has been gained with this procedure, and follow up studies have been published.[2,3,4] Similarly, in an attempt to decrease the morbidity and yet achieve the same results as conventional surgery, Lewis introduced cryosurgery for hemorrhoidal disease. This work also has been submitted to careful review and now follow up studies are available.[6,7] Barron has recently proposed a combination of cryosurgery and elastic band ligation of hemorrhoids.

Armed with the growing information regarding anal dilatation and cryotherapy, it was elected to use the Lord procedure, together with cryosurgery in the treatment of chronic fissure-in-ano. It is emphasized that this represents definitive care, and is not a palliative procedure.

The advantages of cryofissurectomy and anal dilatation are: 1) may be completed under local infiltrative anesthesia, 2) only one day hospitalization is required, 3) lack of postoperative pain, and 4) ability to return to work within three days. There have been no cases of urinary retention in either the fissurectomy or hemorrhoidectomy patients done with cryotherapy. Cryosurgery, like conventional, allows for visualization and precise destruction of tissue.

The physiology of cryosurgery is explained elsewhere.[5] Basically it consists of liquefaction necrosis.

The indications for cryosurgery and anal dilatation are the same as those for conventional surgery. Fissure-in-ano alone or in association with hemorrhoids is treated by this method.

A thorough history is obtained from the patient, and physical examination is carried out prior to cryosurgery. The patient is then briefed on the procedure and advised to expect painless swelling and some drainage.

At the time of surgery the patient is in the left lateral position, no preoperative sedation is given. 30-40 cc. of ½% xylocaine is infiltrated into the perianal area. After anesthesia is obtained, the anal canal is dilated gradually to six fingers size. The anal fissure is identified and with an anal retractor in place, the bed of the fissure is frozen using a cryo-gun for two minutes. The procedure is terminated and the patient sent home the next day with the instructions to take two sitz baths a day, and to wear an absorbent pad as necessary. At the end of one week, the patient returns and the anal canal can easily accept two fingers digital examination. They are then instructed in the daily use of a Young rectal dilator for one month. At the end of this time, all swelling is gone and the fissure site is completely healed.

This technique has been used successfully on twenty patients without complication and without recurrence. There have been no failures to achieve good anesthesia, and no patients have experienced incontinence of stools or flatus.

In conclusion, cryosurgery together with anal dilatation provides a safe, practical method to treat chronic fissure-in-ano.

JOHN J. O'CONNOR, M.D.

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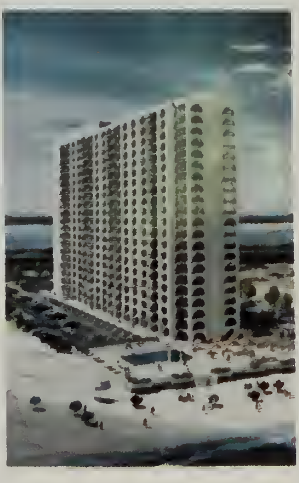

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2. *Lactic Acidosis:* This drug is not recommended in the presence of azotemia or in any clinical situation that predisposes to sustained hypotension that could lead to lactic acidosis. To differentiate lactic acidosis from ketoacidosis, periodic determinations of ketones in the blood and urine should be made in diabetics previously stabilized on phenformin, or phenformin and insulin, who have become unstable. If electrolyte imbalance is suspected, periodic determinations should also be made of electrolytes, pH, and the lactate-pyruvate ratio. The drug should be withdrawn and insulin, when required, and other corrective measures instituted immediately upon the appearance of any metabolic acidosis.
3. *Hypoglycemia:* Although hypoglycemic reactions are rare when phenformin is used alone, every precaution should be observed during the dosage adjustment period particularly when insulin or a sulfonylurea has been given in combination with phenformin.
Adverse Reactions: Principally gastrointestinal, unpleasant metallic taste, continuing to anorexia, nausea and, less frequently, vomiting and diarrhea. Reduce dosage at first sign of these symptoms. In case of vomiting, the drug should be immediately withdrawn. Although rare, urticaria has been reported, as have gastrointestinal symptoms such as anorexia, nausea and vomiting following excessive alcohol intake. B98-146 [illegible]

For complete details, including dosage, see full prescribing information.

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Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American Pharmaceutical Association

"Too many doctors are indif ent to the economic consequence their decisions." So stated a recer issue of *Medical News Report* (De cember 4, 1972), an independent weekly newsletter published by for AMA Chief Executive F. J. L. Blasir game, M.D.

Doctor, are you indifferent...?

In discussing an anticipated i crease in Blue Shield rates, Dr. Bl ingame's newsletter had this to say

"In general, it can be said, M have given the impression they are not particularly concerned with the increase in cost of health care to t patients...

"True, an MD's training is pri marily scientific, but in the real wo of practice, all of his scientific deci sions have a price tag, or an econo impact. The economics of health c beckon the practitioner's attention Concern for economics of medicin

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical Manufacturers Association

When the pharmacist recommends that a drug product other th the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is nece sary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, th unilateral decision of the pharmacis made in the absence of clinical know edge of the patient, could expose hi to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothi in the pro-substitution argument tha offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowledg about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degree puts him at a disadvantage. Most often, a practicing physician will nee expert knowledge of no more than 25

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ld be an obligation of medical
tice . . .
"Medical societies ought to con-
continuing campaigns to point
he substantial savings that could
alized thru deductible insurance
protection for catastrophic ill-
. At the very least, they should, in
patients' interest, question the
cs of any insurance organization
raises health care costs by forc-
olicyholders to buy insurance
may not need or want and prob-
won't ever use.
"Too many doctors are indiffer-
o the economic consequences of
decisions. Too many, for ex-
le, habitually hospitalize patients
e convenience of the MD. It's
ense to deny such habits exist . . .
"Doctors, thru their medical so-
es, have unhesitatingly appealed
eir patients for support in the
against government interference
the private practice of medicine.
the public in the past has re-
ded. It's time the American Med-
Association and state and local
ical societies paid off the debt by
sive action to hold down the cost
edical care."

of Drugs

Insurance rates and hospital
ges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned*. Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

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drugs that he selects to treat the
rity of conditions encountered in
ractice. Moreover, the physi-
's choice of a specific brand is
ed on his knowledge of the pa-
t's medical history and current
dition, and his experiences with
particular manufacturer's
duct.
Some substitution proponents
e argued that the dispensing of a
cription is a simple two-party
saction between the pharmacist
the patient, and that a substitut-
pharmacist may avoid even a
nical breach of contract by simply
fying the patient that he is making
substitution. I would judge that
courts would be sympathetic
ard a pharmacist who substituted
out physician approval and who
ertook a legal defense that seeks
ake the patient responsible for
pharmacist's actions.

uced Prescription Prices?

Substitution advocates are
gesting to the consumer, and par-
larly the consumer activist, that
uced prescription prices could
ow legalization of substitution.
have seen absolutely no evidence
ustify this claim. To the contrary,
erience in Alberta, Canada, where
stitution is authorized, suggests the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands — of, say, ampicillin or tetracycline — or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

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The American Connection: Handguns and Homicide

STEFAN A. PASTERNACK, M.D.*
Discussion by Paul Chodoff, M.D.†

Introduction

It is becoming increasingly clear that the general availability of handguns facilitates the commission of violent crimes. While the vast number of gun owners responsibly use their weapons in non-criminal pursuits, concealed handguns are the predominant weapon of rapists, robbers, assassins, and murderers. Although numerous contributive factors have been implicated in societal violence,[9] the handgun stands out as the primary final agent for injury and death (Table 1). The medical profession, charged with the restoration of health and the preservation of life, should speak responsibly in the growing public debate about the common danger to us all unless effective measures for handgun control are promptly implemented. This paper presents some facts of the "American Connection" between handguns and homicide, and urges restriction of handguns in our society.

TABLE 1
Murder 1970
Types of Weapons Used

Handguns	52%
Rifles	5%
Shotguns	8%
Knives	19%
Other weapons	8%
Body weapons (hand, etc.)	8%

TABLE 2
Murders by Circumstances

Spouse killing spouse	12.1%
Parent killing child	3.1%
Other family killing	8.1%
Romantic triangle & lovers quarrels	7.1%
Other social arguments	40.8%
Sub Total	71.2%
Known felony	20.4%
Suspected felony	8.4%
Total	100%

The Facts of Homicide

Most Americans are blind to the banal realities of homicide. Dazzled by detective stories and misled by gangster movies, the public is under the misconception that murder is the work of criminal masterminds who kill to achieve profit and power. The psychiatric study of homicide reveals the exact opposite to be true. Homicide is a simple-minded deed. Most murders are *not* associated with the commission of felonious crimes. Most murders are *not* the result of Mafia type contracts perpetrated in the name of criminal organization.

In 1972, as in years past, approximately 70% of all homicides were committed by relatives of the victims or by the victims close personal acquaintances (Table 2). It is startling to realize that if all known criminals were immediately imprisoned we would continue to witness an increase in murder. The majority of murders occur in private homes, within social circumstances, and homicide is, to a major extent, "a national social problem beyond police prevention."[6] While a significant number (25%) of homicides are committed by known criminals, a majority of homicides are committed by usually law abiding citizens who are not consciously intent upon murder. Such persons inadvertently become killers when, during a temporary explosion of anger, they utilize a dangerous weapon as a means of expressing hostility. Certain life experiences and developmental patterns have been linked with "violence proneness," but have not been of great use in preventing dangerous behavior.[2,3,8,10] Other factors are tabulated in Table 3. It is clear, however, that any person, even without serious pre-disposing factors, can be caught in a crushing existential trap from which he may seek escape by homicide. Subjected to sufficient stress, most persons revert to primitive thinking patterns characterized by inordinate fear of attack, feelings of vulnerability and insecurity, and increasing anxiety. The hallmarks of someone who is losing control over violent impulses have been described[10] and reflect the progressive emotional decompensation of someone caught in a bitter conflict within himself and with others for which he fails to find a peaceful resolution. All too often an unwitting victim continues to provoke the person who is on the verge of explosion. *Case 1:* A 40 year old truckdriver had beaten his girlfriend when he learned that she had an affair during his recent absence. Upon his return from another road trip, she presented him with a pistol as a gift. Two days later, during a fight over her renewed amorous interest in another man, he beat her and shot her in each hand and leg. She crawled to safety when a neighbor intervened. She subsequently withdrew all charges and married him three months later.

---

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There is increasing awareness that sadomasochistic pairing of would-be victim and would-be assailant precedes violent outbursts.

Studies of victimology[15] reveal the presence of a violence-instigating person who ignores good sense by harassing the one who then attacks. The victim-offender relationship is now routinely considered in many pre-trial reports involving homicide and assault. Some victims desire injury and their wounds may be considered the price they are willing to pay so that they can inflict guilt upon their assailant. Such dynamics pertain particularly to the sado-masochistic couple, often alcoholic, who unwittingly overstep their previously controlled hostility threshold. The separation and disarmament of fighting couples may save lives.

TABLE 3

A Checklist of Factors in the Evaluation of the Dangerousness of the Mentally Ill

I. CHILDHOOD FACTORS
  - A. History of parental brutality with brutal beatings
    This may be in the form of excessive punishment, violent reprisals for mistakes.
  - B. Parental seduction
  - C. Organic brain damage with abnormal EEG
  - D. Childhood schizophrenia
  - E. Preoccupation with death and killing
  - F. Compulsive fire setting
  - G. Cruelty to animals, sadism, torture of "pets" (If any, was there any parental punishment?)
  - H. Enuresis
  - I. School and learning difficulties
  - J. Personal experience with violent death
  - K. Family instability, criminality, mental disorder and poverty
  - L. Erratic control over violent impulses
  - M. Chromosomal abnormalities

II. PERSONALITY STYLES, PERSONALITY DYNAMICS
  - A. General sense of inadequacy and fear of failure
  - B. Intense ambivalence with tendency towards projection
  - C. Lack of social ability with schizoid tendencies
  - D. Poor impulse control–poor ergo delaying mechanisms
  - E. Difficulty utilizing leisure time pleasurably
  - F. Sado-masochistic relationships with frequent frictional encounters between roommates, lover, spouses, relatives, etc.
  - G. Prevalence of primary process over secondary process
  - H. Faulty reality testing
  - I. Easily and irrationally triggered violence
  - J. "Potential readiness" to strike out at others, based on need, wish to injure figure from the past (murder transference)
  - K. "Fugue" states, blurred consciousness

III. MISCELLANEOUS FACTORS
  - 1. Conspicuous accounts of fist fights, violent acting out
  - 2. Penchant for guns and knives
  - 3. History of alcoholism
  - 4. Unusual tattoos with violent themes
  - 5. Drug abuse
  - 6. Police arrests, prior episodes of violent behavior
  - 7. History of attempted suicide (inversely related to homicide)

While murder has been associated with a wide variety of clinical states, murder by acutely psychotic persons is rare.[12] The clinical state most often discovered in someone who has committed a homicide not in conjunction with a felonious crime is variously described as "dissociative homicide."[10,11,12] This reflects the sudden breakdown of emotional controls and the uncontrolled expression of murderous rage. Such emotional disruption is transient, often facilitated by drugs or alcohol, provoked by passion, and followed by remorse.

In most instances the murderer sought only to hurt his victim and suffers guilt at his violation of the commandment "Thou shalt not kill." Murder is in violation of his own moral code; it is "ego dystonic." This is in marked contradistinction to the hardened criminal who consciously accepts murder as a means towards his criminal ends. For such criminals, murder is "ego syntonic," not in conflict with their sociopathic moral code.

The tragedy is evident: when one brandishes a gun during a social altercation, one may inadvertently become a killer. While anyone who draws a weapon during arguments must be considered unwise, reckless, lacking in judgment, and irresponsible in the expression of his hostility, the role of the gun must be implicated as well. The ready availability of handguns makes it more likely that they will be used unwisely and recklessly. *Case 2:* A 25 year old man brooded over marital problems and an inability to get ahead in his job. He projected his anger onto his wife, whom he secretly suspected of infidelity. He drank to relieve his mounting tension. She quarreled with him regarding his progressive alcoholism and during an angry confrontation he threatened to beat her. She threatened to leave him. To "teach her a lesson," he pulled out his gun from a nightstand and shot her. She died. He later denied intent to kill, insisting, "I only wanted to stop her from leaving, to hurt her."

The Unique Role of the Gun

The handgun is the primary weapon in the commission of violent crimes in the United States. During this century over 800,000 Americans have been gunned down. On a typical day someone is wounded or killed by gunshot every ninety seconds.[1,6] Assassins used handguns in nine of the ten attempts on the lives of Presidents or presidential candidates. Assailants with concealed handguns killed over 460 officers of the law in the last 10 years and the rate of police fatality is rising.[8] Similarly, the homicide rate has risen dramatically and over 20,000 persons are homicide victims each year: homicide is the seventh leading cause of death among non-white males of all ages ranking second only to accidents in the deaths of both Black and white males ages 15 to 24.[7] Closer to home is the statistic that as many physicians are murdered as die of duodenal ulcer.[12] Since homicide is a major cause of death, it is clearly worthwhile to make some attempt to control those factors which increase the likelihood of homicide. The availability of the handgun is a primary factor, with its extra-ordinary lethality, and accounts for a majority of killings. The knife has only 1/5th the lethality of the handgun, and studies repeatedly show that when a gun is used to inflict injury the victim is more likely to die than if injured by any other weapon. Handguns are easily used. Even persons protected by body guards are prey for a persons with a handgun, since handguns are easily concealed and allow an assailant to surprise his victim with little chance for escape. One can not stop a bullet as one can stop a knife. Guns permit persons who lack power or strength themselves to achieve "lethal power" at a distance from the victim. The assailant does not so readily observe his victim's pain, there is no body contact, there is little time to reconsider, there is no time for tears and little time for mercy. There is good ethologic evidence to suggest that mankind has developed some biologic inhibition against the use of his body for murder. While fist fights are frequent, they are rarely fatal, and stomping and kicking are infrequent methods of murder. Strangulation rarely results in homicide, although it is a frequently used method of attack: assailants usually "come to their senses" as they stare into the cyanotic faces of their victims, and others witnessing the attack have time to intervene. Humans do not use their canine teeth to kill, although one could easily bite through another person's jugular vein. It is clear that in the absence of guns, less dangerous discharges of hostility would occur. Instead of a corpse, we would only have a victim with injured pride and possibly a broken nose. Above all, handgun murders are possible because guns are plentiful: over 10,000,000 were sold in the last 10 years, and over 50,000,000 are in homes throughout the nation.[9] When tempers flare, gone for the moment are any thoughts of restraint, arrest or punishment. The only thought is to strike out. When a gun is used, the possibility of death rises sharply.

The lethality of the handgun is also tragically evident in the increasing number of accidental death from firearms. While the majority of gun owners use their weapons responsibly, the data, locally and nationally, indicate a rise in firearms death.[9] The rate of accidential firearms deaths parallels by geographical area the known pattern of gun ownership. More guns result in more gun accidents: *Case 3:* A suburban housewife became alarmed at reports of increasing assaults and purchased a handgun after a neighbor's home was burglarized. Several days later, her five year old son found the pistol which was kept in a night table drawer. He died of a fatal wound when he fired the gun.

The Motivation to Acquire Handguns

A random sampling of Americans reveals many stated reasons for acquiring guns:

> "I want protection against burglars." (an inner-city resident)
>
> "I am afraid of riots and civil disorder." (an inner-city resident)
>
> "I have been frightened by a robber." (a suburban home owner)
>
> "I always have guns; I grew up with them." (a suburban home owner)
>
> "It was a family heirloom." (a rural home owner)
>
> "I shoot in competitive matches and like guns." (a suburban worker)
>
> "In case I ever need one." (an apartment dweller)

In spite of the apparent reasonableness of many of the stated motives, a frequent discovery is that in a majority of instances, Americans are buying guns on the basis of powerful, unconscious motives. Such gun purchases are then rationalized with utilitarian explanations. Most Americans who buy guns out of fear fail to consider other possible non-lethal alternatives. Many persons acquire handguns in the attempt to master deep-seated feelings of anger and frustration. *Case 4:* A 42 year old businessman felt discontented in his marriage and was frustrated by his disobedient teenagers who abused drugs. He felt helpless to control or to influence their behavior and could not tolerate the loss of "respect" shown him. Although he lived and worked in a safe suburban community, he came to fear "attack from elements." He purchased a pistol for self-protection. Unaware of his mounting hostility at his family, he projected his anger and instead saw danger from others while becoming a danger himself. He enjoyed his pistol and became a marksman. He felt a new sense of power. During an angry confrontation with his son he brandished his weapon and shot him in the leg. His family life remains perverted by a profound sense of danger, distrust, and hatred.

Others purchase guns to compensate for real physical deficiences. *Case 5:* A 20 year old man feared defeat by a rival whom he could not physically overpower. He purchased a gun as an "equalizer" before the appointed hour of their struggle. He was then ready for "anything," and as if in a Western draw, he shot his opponent.

Guns themselves are seductive and aggressive stimuli which may give expression to the owner's repressed and unacceptable sexual feelings, and/or fear of impotency. Guns encourage violent solutions of life problems. When a gun is bought in need, a need is soon found for its use. Perhaps the greatest folly of all is the illusionary purchase of guns for "household defense."

Household Firearms: False Insurance

Many Americans, over-responding to fears of burglars and intruders, succumb to the false logic that if they are armed with a handgun they will insure the safety of their homes. The facts expose the fallacy of such thinking. Studies of the National Commission of Violence, showed that far more *homeowners* were killed in gun accidents than were killed by burglars and robbers during a 4½ year study. Furthermore, experiences of armed citizens reveal that they are usually taken by surprise and are unable to get to their weapons. He who tries to draw on a man already holding a weapon is likely to die. The "armed household" concept does not appear to have deterred intruders as the rising statistics of suburban crime show. Household arms do, however, provide criminals with a ready arsenal of weapons. A large number of guns subsequently recovered by police after arrest of criminals were stolen from homes. Home handguns are poor insurance against intruders and may endanger the very person they were purchased to protect. *Case 6:* A Bethesda businessman was aiding his teenage son to load his newspapers into a car when they were confronted outside his home by two men wielding knives. They forced the man and his son into the home where they found a rifle and two pistols which they seized. They then fled with the weapons and a small sum of money.

The Gun Control Debate: Unfortunate Invective and the Pursuit of Compromises

There is increasing national sentiment for some form of handgun control. The President has addressed the problem by seeking measures to restrict the sale of "Saturday night specials." The vicious cycle of Americans arming to protect themselves against other armed Americans must be interrupted. The assassinations of President Kennedy, Senator Kennedy, Martin Luther King, the attempted assassination of Governor George Wallace and the more recent street shooting of Senator Stennis dramatize the dangerousness of the current situation for our national political life. For many years, an intense debate has raged between "gun lobbyists" and the "abolitionists" in the search for a rational handgun policy. Tragically the debates have generated more heat than logic. It is clear that bona fide sporting enthusiasts and hunters should have access to the long guns and handguns they use in competitive marksmanship contests and in hunting. It should still be possible to reduce the availability of handguns without interferring with legitimate gun sports. Compromises should be possible through wise leadership. How to do this will require legislative skill on the part of duly elected officials. But unless such officials feel the support of the voting public it is unlikely that they will risk incurring the wrath of the politically effective National Rifle Association which has in the past mustered its members in dramatic opposition to *any* form of gun control. The efforts of the D.C. Medical Society to encourage gun laws which will reduce handgun circulation may embolden otherwise apathetic political leaders. The time has come for the American Medical Association to endorse enactment on a national level of gun control legislation.[4] The matter however is urgent as the spread of handguns through our society continues, now increasingly reaching even into our secondary schools.

High School Homicide and Handgun Pushers

A new and more disturbing chapter in "Homicidology" began with the shooting deaths of four high school students in the recent past. Just as drugs have spread from criminal users to our school children, it is becoming clear that "gun pushers" are at work selling cheap weapons to those whom they can tempt with the promise of firepower. Usually of the cheap "Saturday night special variety," such weapons have been implicated in shooting deaths in many metropolitan areas.[14] *Case 7:* A 17 year old student collided with another youth in a city high school. While he was attempting to apologize the other student pulled a pistol and shot him. There was no warning. When arrested the assailant could not explain why he shot the other student. He gave no reason for coming to school armed other than "to protect myself."

It is difficult enough for teachers and students to work together under the pressure of racial tension, political discord, and budgetary uncertainty. The fear engendered by shooting deaths only further disrupts the already undermined academic institutions. When guns are so plentiful that they are being found in significant numbers in high schools, is it not time for their restriction?

Conclusion

The primary etiologic role of the handgun in the commission of homicide has been reviewed. The danger to the individual citizen, the police officer, the homeowner, the political leader, the school student, has been described. Data regarding "involuntary dissociative homicide" and factors relevant to "violence proneness," have been reviewed. It is clear that the complex intra-psychic, interpersonal, and sociocultural factors which foster violence can not be rapidly or easily modified. Hence it is logical to direct preventive efforts at the primary etiologic agent, the handgun. It is incontrovertible that where there are fewer guns there is less violence.[8] The solution to the problem of gun violence should be urgently pursued at a national level.

The solution requires the active participation and leadership of the medical profession.

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Comment On A Paper By Dr. Pasternack

Dr. Pasternack's excellent paper documents with illuminating detail the extremely grave nature of the "plague of guns" with which this country has been afflicted. He also makes it clear that the medical aspects of the problem are so significant that no doctor can afford to ignore them as falling outside of his professional purview. As mentioned in Dr. Pasternack's article the Medical Society of D.C. can take pride in the fact that it has been in the forefront of efforts to produce a national consensus on this subject within organized medicine and specifically to infuence the AMA to take an active position in favor of U.S. Congressional action in favor of more effective regulation of the manufacture, sale and illegal possession of firearms.

As readers of the Medical Annals of D.C. know, in April, 1972, a questionnaire submitted to members of the Medical Society of D.C. elicited overwhelming support for more stringent gun control laws. The membership also voted very strongly in favor of presenting an appropriate resolution to the meeting of the AMA in June, 1972. This was done but at that meeting the resolution was not approved in spite of the vigorous efforts of Dr. Crain and Dr. Burka. It can now be reported that a similar questionnaire submitted to the membership of the Montgomery County Medical Society in April, 1973 has been answered overwhelmingly in favor of gun control by legislative means.

Under the leadership of Dr. Burka, the Medical Society of D.C. is again introducing a gun control resolution at the AMA Meeting in June, 1973. The thrust of our effort will be to place the emphasis on the control of handguns which are the chief agent of the wanton and violent destruction of human life and health which firearms are causing in this country. The resolution to be introduced, and which we hope will receive the active support of the members of the Medical Society of D.C. and of all concerned physicians throughout the country is as follows:

Whereas bodily injury and homicide resulting from the illegal use of firearms have reached epidemic proportions in this country and now constitute a major public health hazard, and

Whereas the majority of such homicides occur by the use of handguns in the course of quarrels among friends and members of the same family in a state of temporary excitement or emotional imbalance, and are thus not amenable to ordinary law enforcement procedures

Therefore be it Resolved:

That the American Medical Association urge the Congress of the United States to enact legislation providing for the strict control of the manufacture, possession, acquisition and transfer of handguns through regulations that protect the overall public interest while safeguarding the rights and privileges of those who are qualified to keep and use handguns safely and responsibly.

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Giardiasis in Young Adults*

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Abstract

Giardia lamblia was identified in stool samples of 5 university students. Four students were symptomatic with various combinations of diarrhea, nausea, anorexia, abdominal bloating, and epigastric tenderness. Although infection with this protozoan is usually associated with foreign travel, 2 of the students had never been outside the United States. Response to treatment with Atabrine or Flagyl led to rapid relief of symptoms.

Introduction

The protozoan Giardia lamblia, once thought to be an insignificant finding in the fecal flora, has been increasingly incriminated as a cause of acute and chronic gastrointestinal illness. A wide spectrum of disease is involved, ranging from mild acute diarrhea[1] to servere and debilitating chronic malabsorption.[2]

Stools for ova and parasites were examined by the direct smear-iodine stain method on all patients seen at the Georgetown University Student Health Service for any unexplained gastrointestinal illness of more than 48 hours duration. Giardia lamblia was identified in five students over an eight month period. Although Giardia is acquired primarily during foreign travel[3], this report emphasizes that it may also be found in healthy young adults who have never left the United States.

Case Reports

Case 1: J. Z., a 26 year old law student, left California and drove across the United States over a three week period. He camped at night, usually in public camp grounds, and prepared most of his own food. In the Rocky Mountain states he swam in mountain streams and drank untreated water from the streams. About 10 days before he reached Washington D.C. diarrhea began. By the end of his trip he was having five watery bowel movements daily, had a poor appetite, and had lost 10 pounds. The diarrhea was never bloody, he had no nausea or vomiting, and no fever. His physical examination after two weeks of symptoms was normal except for moderately severe epigastric tenderness. Stool specimens were loaded with Giardia lamblia cysts. Stool culture, complete blood count, and liver function tests were all normal. He was treated with Atabrine 100 mg t.i.d. for four days, with disappearance of all symptoms. Two weeks later watery diarrhea and epigastric pain recurred and a single stool specimen again contained numerous Giardia cysts. He recovered during a 10 day course of treatment with Flagyl 250 mg t.i.d. and has remained well for six months.

Case 2: N. H., a 27 year old graduate student from Cambodia, reported to the Student Health Service because of epigastric pain of three days duration. The pain was severe enough to awaken her at night and became much worse after meals. She had no nausea or vomiting, and no diarrhea. Her only other symptom was severe generalized headache. The physical examination revealed only epigastric tenderness to palpation. X-rays of the upper gastrointestinal tract were normal. Stool samples contained many Giardia lamblia cysts. After one week of Atabrine 100 mg t.i.d., stools became negative and the epigastric pain stopped.

Case 3: P. B., a 20 year old undergraduate who had never been outside the United States, developed nausea, abdominal pain, and a sensation of severe bloating after food ingestion. Because of these symptoms he was unable to eat. Watery diarrhea occurred two to three times daily, and was associated with severe headache. He had traveled from Massachusetts to South Carolina during his winter vacation, but for six weeks prior to onset of his illness he had remained in Washington, D.C. Physical examination one week after symptoms first

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CLINICAL DATA FOR PATIENTS WITH GIARDIASIS

	AGE	SEX	HISTORY	DIARRHEA	PHYSICAL EXAM.	TRAVEL
1.	26	M	Two weeks of diarrhea, anorexia, 10 lb. weight loss	5x daily Watery	Epigastric tenderness	U.S. cross country trip
2.	27	F	Three days of epigastric pain after meals and at night; headache	No	Epigastric tenderness	Arrived from Cambodia 1 week before onset of symptoms
3.	20	M	One week of nausea, abdominal aches and bloating after meals; headache	2-3x daily Watery	Right upper quadrant tenderness	Massachusetts South Carolina Washington, D.C.
4.	23	M	Two days of nausea, anorexia; headache	No	Normal	Arrived from Libya 2 months before onset of symptoms
5.	30	F	Passed large worm (Ascaris) in stool	No	Normal	Venezuela 1 year before

developed revealed only right upper quadrant tenderness to palpation. Stool culture, blood count, and liver function tests were normal. A stool sample revealed numerous Giardia cysts. He recovered after one week of treatment with Atabrine 100 mg t.i.d.

Case 4: M. D., a 23 year old student, became ill two months after he emigrated to the United States from Libya. He complained of nausea, anorexia, and occipital headache, but experienced no vomiting and no diarrhea. Physical examination was normal. Stool samples contained Giardia lamblia and Endolimax nana. He recovered after three days of Atabrine treatment, 100 mg t.i.d.

Case 5: J. L., a 30 year old graduate student, visited the Student Health Service after she passed a large white worm in her stool. She was completely asymptomatic. During a tour with the Peace Corps in Venezuela she had been treated one year previously for Ascaris infection. Besides Ascaris, the present stool specimen also contained Giardia lamblia and Endolimax nana. She was treated only for the Ascaris, with thiobendazole.

Thus, previously described symptoms of acute giardiasis were found in several of our patients (Table 1). Two of the five had watery diarrhea, two had nausea, and two had abdominal pain with bloating, exacerbated by food intake. In addition, three of the patients complained of rather severe headache. The only physical finding was upper abdominal tenderness, in three of our five patients.

Discussion

The acute form of giardiasis, consisting of abdominal pain, bloating, nausea, anorexia, and diarrhea, occurs approximately 10 to 14 days after infestation[1]. Less frequently, chronic diarrhea and malabsorption syndrome may last for months or even years before diagnosis of giardiasis is made[2] Giardia lamblia may occasionally be found in the stool of asymptomatic carriers, as it was in our Case 5.

Infection with Giardia lamblia has been especially frequent in patients with dysgammaglobulinemia[4], and isolated deficiency of duodenal secretory IgA has been demonstrated in patients with chronic giardiasis[5]. Patients with preexisting organic gastrointestinal disease such as peptic, ulcer, cirrhosis, pancreatitis, and gastrectomy, also seem especially susceptible to giardiasis[6]. In healthy patients, the onset of acute giardiasis may result from exposure to contaminated water supplies or from direct fecal ingestion. Poor sanitation in other parts of the world accounts for most giardiasis diagnosed in the United States. For instance, of 70 patients with giardiasis at a California clinic, 83% had been travelling outside the United States during onset of symptoms[3]. Acquisition of the disease is not limited to tropical climates; several outbreaks have resulted among members of group tours to the Soviet Union[7]. Two of our patients were foreign students, recently arrived from Cambodia and Libya respectively, and one of the American patients had served in the Peace Corps. All had lived under conditions where Giardia might be present. However, the other two patients had never been outside the United States, and had less obvious reason for exposure to Giardia.

Outbreaks of giardiasis have occasionally occurred in the United States. In 1965-66 numerous vacationers at ski resorts in Aspen, Colorado developed diarrhea and 59 of them were found to excrete Giardia cysts[8]. The epidemic was eventually traced to sewage contamination of the water supply. Endemic Giardia, with occasional outbreaks of illness, has also been found in large institutions in the United States, especially among retarded patients. Direct fecal ingestion is felt to be the mode of transmission[9]. The exact source of infection in our two patients without a foreign travel history remains obscure. One had ample exposure to possibly contaminated water at campgrounds across the United States, and drank untreated water from mountain streams as well. The other travelled along the eastern coast but remained in Washington D.C. for six weeks before the onset of his illness. He did not knowingly drink from any untreated water supply; meals were taken with family, friends, or in the college dining hall. He knew no one with similar symptoms, and stool examinations of friends and dining hall acquaintances were negative.

The life cycle of Giardia lamblia helps explain both the symptoms and the occasional difficulty in diagnosis. The trophozoite form of the protozoan resides in the duodenum, where it is adherent to the epithelial surface and may actually invade the mucosa[10]. Conversion to cysts, the form found in the stool, occurs lower in the small intestine. Infestation of the duodenum may result in anorexia, nausea, vomiting, and upper abdominal pain and tenderness. These symptoms were present in three of our patients. Unexplained severe epigastric pain, following meat ingestion, has also been reported[11]. X-rays may demonstrate spasm and irritability along with thick blunted mucosal folds in the small intestine[12], although the one patient studied in this series had normal gastrointestinal films. In all of our patients numerous cysts were easily found in stool samples examined by a direct smear stained with iodine. This has been the experience of others in diagnosing acute giardiasis[1]. However, in chronic giardiasis, cysts may be shed only periodically, and numerous stool examinations might be negative. In such cases, examination of duodenal aspirates for the trophozoite form[13] or touch preparations of duodenal biopsy specimens[2] may be necessary for diagnosis.

Treatment of giardiasis in adults may be achieved with either Atabrine 100 mg t.i.d. or Flagyl 250 mg t.i.d.[14]. Previous recommendations for only three to five days of treatment with Atabrine will lead to a significant number of relapses, so that Atabrine should be continued for one week. If Flagyl is chosen, the course of therapy should be seven to ten days.

Summary

Investigation of unexplained nausea, anorexia or weight loss, epigastric pain or bloating, and watery diarrhea, not necessarily occurring together, should include examination of three separate stool samples for Giardia lamblia. In cases of chronic diarrhea and malabsorption, negative stool examination should be followed by aspiration of duodenal contents to search for the trophozoite form of Giardia. The disease is common among travelers to foreign countries but may also occur in patients who have never been outside the United States.

Acknowledgment

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An Epidemiologic Study of Gonorrhea and Cancer of the Prostate Gland

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Synopsis—Abstract

Trends in age specific mortality rates from prostatic cancer in the United States could be explained by exposure to a carcinogenic condition that stopped sometime in the past. It is hypothesized that gonococcal infection in the pre-chemotherapy pre-antibiotic times and the resultant iatrogenic complications may be related to development of cancer of the prostate later in life. Death rate curves for prostatic cancer and incidence curves for gonorrhea in Denmark match well with a lag period of 45 years. Spectral analysis gave a lag period of 42 years and a coherence coefficient that differed from zero at level $p < .05$.

If the relationship demonstrated in this paper is of causal nature, one could predict a continuing decline of mortality from prostatic cancer due to attrition of the cohort that received the old treatment.

Introduction

There was very limited progress in the treatment of gonorrhea from 1892, when Janet introduced potassium permanganate solutions for urethral irrigation, to 1936 when the modern era of chemotherapy and antibiotics started with the clinical use of sulfanilamide. Urethral irrigation with astringent solutions and the use of catheters and bougies for treatment of gonorrhea and its complications was inadequate to eradicate gonococci and often resulted in irritation, traumatization and secondary infection. Extension of infection to the posterior urethra and involvement of the prostate and seminal vesicles was quite common. (1) Thus, many gonococcal infections ended in chronic prostatitis. With the advent of antimicrobial therapy, the incidence of posterior urethritis, prostatitis, vesiculitis and epididymitis remarkably declined[1,2,3].

Chronic infection and chronic irritation as a possible source of cancer in man has been well documented. Squamous cell carcinoma of the skin around chronic sinuses of osteomyelitis, carcinoma of the gingiva in the vicinity of an ill-fitting denture, and transitional or squamous cell carcinoma of the urinary bladder arising on the basis of Schistosomal cystitis are but a few examples[4,5,6]. Moreover inflammation plays a significant role in the pathogenesis of prostatic atrophy and histologic studies showed the development of prostatic carcinoma from areas of atrophy and regeneration in the peripheral part of the gland[7].

In a study conducted by Steel in Canada, a past history of venereal diseases was reported by more patients with prostatic cancer (12.8%) than patients in the two groups of general controls and benign prostatic hyperplasia (2.5% and 5.7% respectively),[8]. (2)

The present investigation attempts to test a hypothesis that links gonorrheal infection in the pre-chemotherapy era with the development of cancer of the prostate later in life.

Materials and Methods

Age specific death rates for cancer of the prostate, pancreas and lung were computed from Vital Statistics of the United States for the period 1937 to 1967, and trends of mortality from cancer of the three sites were compared[9]. Two methods were used to assess the relationship between gonorrheal infection and development of prostatic cancer: the empiric (graphic) method and the time series analysis

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[1] Potassium permanganate, acriflavin, protergol, mercury oxycyanide, picric acid and silver nitrate were used for urethral irrigation.

[2] Conclusions drawn from this study should be accepted with caution because it involved only 39 prostatic cancer patients.

method (spectral analysis).

The mortality from prostatic cancer (1941 to 1970) and the incidence of gonorrhea (1891 to 1940) were obtained from the National Health Service of Denmark. Then the curve for death rates from cancer of the prostate per 100,000 males 50 years of age and over was superimposed and matched with that of incidence rates of gonorrhea per 100,000 males 14 to 65 years of age. (3)

A time series may be defined as a set of random responses occurring over time. Observed gonorrhea incidence rates and cancer death rates may thus be considered as realizations of time series. In this study, gonorrhea incidence rates are referred to as "input" series and prostatic cancer death rates are referred to as "output" series. If the frequencies comprising the gonorrhea series of incidence rates are transmitted to the cancer series of death rates so that the same frequencies are represented in the latter series, then the two series are said to have high coherence. If, on the other hand, extraneous factors influence the cancer series in a random unpredictable manner, then the cancer series will have frequency components not present in the gonorrhea series and the two series will lack coherence. The parameter γ (f), the coherence coefficient at dominant frequency f., ranges from 0 to 1, 0 representing an output series with frequencies resulting solely from extraneous factors and 1 representing an output series with frequencies corresponding precisely with the input series. Thus, estimation of coherence coefficient will enable us to assess the strength of the relationship between the gonorrhea series and the prostate cancer output series.

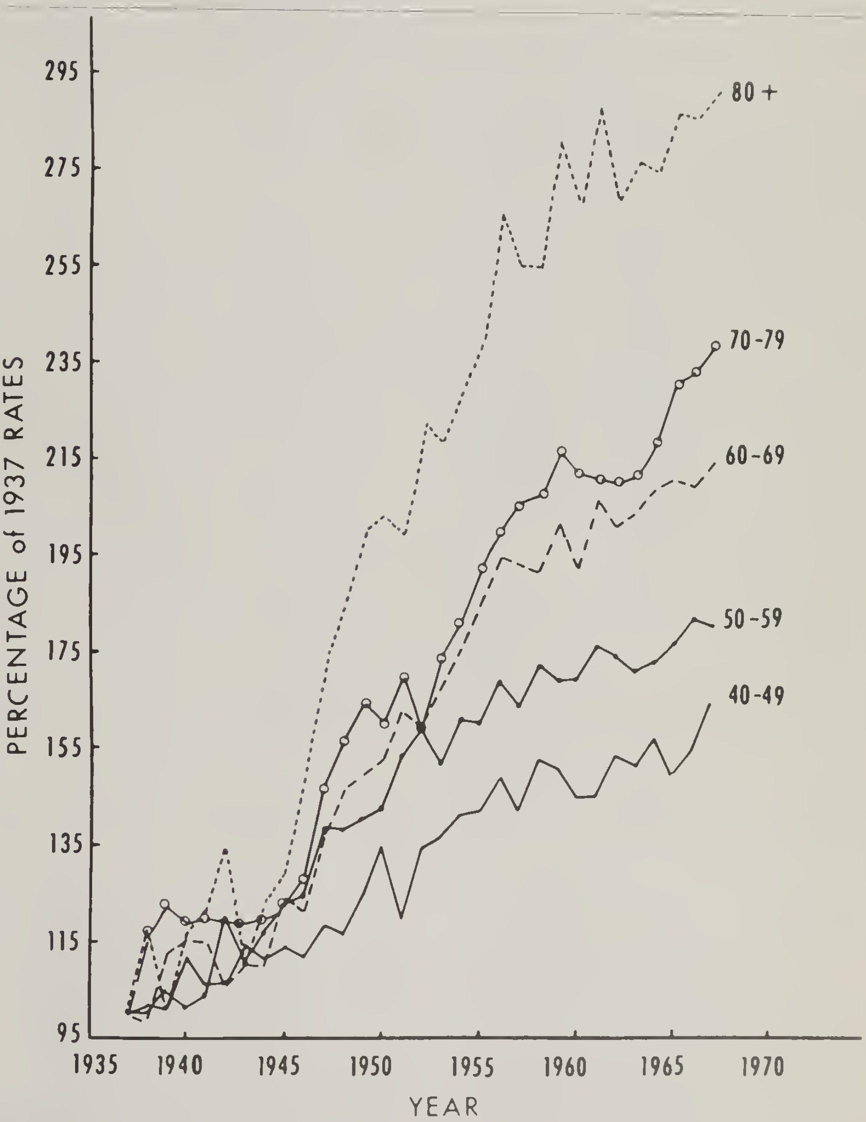

FIG. 1. Percentage of 1937 age specific death rates from cancer of the pancreas, per 100,000 population, U.S.A. 1937-1967.

When two time series have the same dominant frequency, the "lag" of the output series behind the input is expressed as the difference between phase angles of two sine curves, which is equivalent to the difference in years of the points at which two sine waves peak. The lag between a gonorrhea series and a prostate cancer series is analogous to the latent period between contact with gonorrhea and onset of prostate cancer.

Time series analysis in this study was performed using the UCLA Biomedical Computer Program BMD02T (Autocovariance and Power Spectral Analysis) on the IBM 360/50 computer at Howard University Data Processing Center[10,11].

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[3] During the period 1941-1970 while over 70% of the population were under 50 years, only 0.54% of all prostatic cancer deaths occurred before the fiftieth birthday. This fact makes death rates computed per 100,000 population a poor index for illustrating trends of mortality from cancer of the prostrate because minor changes in mortality over time would be masked by the large number of people below 50 years and by fluctuations in this sector of the population from year to year.

Results and Discussion

Death rates for cancer of the pancreas, lung and prostate for age groups 40 years and over, 1937 to 1967, are shown in figures 1, 2 and 3 respectively. While rates for cancer of the pancreas and lung have been steadily increasing since 1937 in all age groups, those for cancer of the prostate show a different pattern. Rates for the cohort 80 years and over show remarkable increase over time, those for the 70 to 79 year cohort have also increased, but to a much lesser extent and those for age groups below 60 have declined and the slope is greater in younger than in older age groups.

If exposure to carcinogenic factors is etiologically related to development of cancer of the above mentioned sites, the pattern for cancer of the pancreas and lung could be explained by a dose-effect relationship over time. Older age groups, having longer periods of exposure, show the greatest increase in death rates, and rate of increase diminishes with succession of younger age groups. The continuing rise of death rates in the youngest age group (40 to 49) indicates that more and more individuals who had been exposed are dying and the after-effect of the carcinogen is still operating. In contrast, the steady decline in death rates from cancer of the prostate in age groups below 60 years indicate that exposure to the carcinogenic factor had stopped at some past point in time and the impact of that factor is fading away in younger age groups.

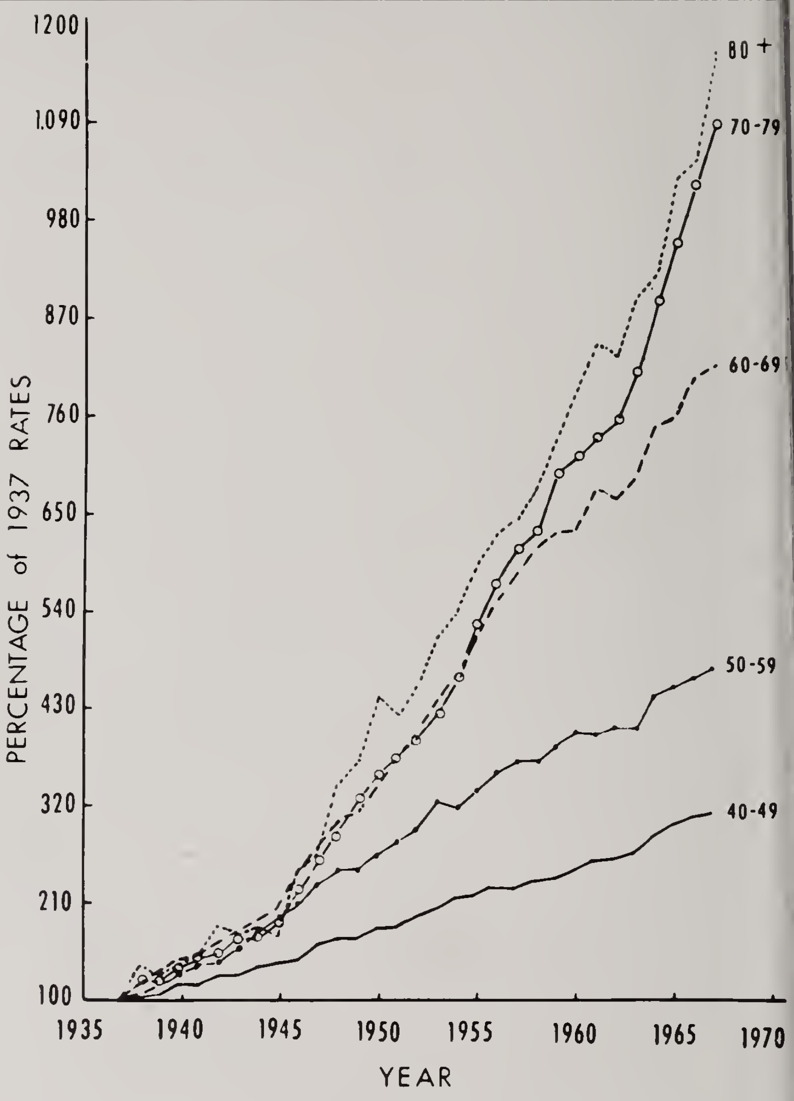

FIG. 2. Percentage of 1937 age specific death rates from cancer of the lung, bronchus and trachea, per 100,000 population, U.S.A. 1937-1967.

Explaining the trends shown in figure 3 in the context of gonorrheal infection, the cohort 80 years plus in 1967 showed marked increase in mortality from prostatic cancer because it was 49 years plus in 1936 (beginning of chemotherapy) and its members had spent almost all the period of their exposure to gonorrhea (15 to 50) in the preantimicrobial era. (4) Age group 40 to 49 years showed the greatest decline in mortality because it was 9 to 18 years in 1936 and majority of its members were, at that time, below the age of 15. Mortality curves for other age groups arranged themselves between these two limits according to years of exposure to pre-chemotherapy gonorrhea.

Annual mortality rates from cancer of the prostate for a period of time and incidence of gonorrhea in males for a similar period, with a reasonable time lag, was needed to investigate this matter further. Unfortunately, national reporting of gonorrhea by age and sex in the United States started after 1939. The health departments of Sweden, Denmark and Finland were contacted to get the needed data.

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[4] California was among the pioneer states to report gonorrhea by age. In 1937, only 3.3% of cases occurred before the age of 15 and after 50 years. Even 30 years later (1967) the corresponding figure for the whole nation did not exceed 2.5% (12).

TABLE 1

Incidence of gonorrhea per 100,000 males 15-64 years of age, 1896-1931, and deaths per 100,000 males 50 years and older, 1941-1970.*
(Denmark)

GONORRHEA				CANCER OF THE PROSTATE			
Year	Rate	Year	Rate	Year	Rate	Year	Rate
1896	600.6	1914	993.2	1941	41.1	1959	80.9
1897	648.8	1915	1,023.8	1942	41.7	1960	74.5
1898	647.3	1916	1,012.5	1943	40.1	1961	78.5
1899	617.6	1917	1,010.4	1944	37.5	1962	83.4
1900	664.9	1918	1,240.2	1945	35.4	1963	83.0
1901	719.3	1919	1,231.4	1946	44.2	1964	86.3
1902	714.3	1920	947.9	1947	44.0	1965	86.3
1903	717.0	1921	888.5	1948	48.8	1966	72.7
1904	673.0	1922	819.2	1949	47.3	1967	70.5
1905	648.7	1923	839.9	1950	48.1	1968	71.4
1906	719.3	1924	811.3	1951	51.9	1969	75.0
1907	844.7	1925	835.5	1952	58.8	1970	67.3
1908	917.6	1926	870.5	1953	76.4		
1909	879.2	1927	797.3	1954	64.8		
1910	850.6	1928	792.3	1955	74.2		
1911	914.7	1929	743.1	1956	75.3		
1912	828.8	1930	746.3	1957	74.7		
1913	873.8	1931	667.6	1958	77.0		

* Computed from data mailed to authors by officials of the National Health Service of Denmark on October 16, and November 8, 1972.

Denmark was the only country that had incidence figures for gonorrhea, by age and sex, from as early as 1877 till the present.

Table 1 lists age and sex specific incidence rates for gonorrhea, 1895 to 1931, and mortality rates from cancer of the prostate, 1941 to 1970, as computed from data made available to the authors by the National Health Services of Denmark. (5)

Figure 4 was obtained by sliding and fitting of gonorrhea incidence and prostatic cancer mortality rates and illustrated a lag period of 45 years between the two diseases. (6) This empirical estimation procedure, for the lag period, was then applied to the "detrended" data, i.e., the residuals of gonorrhea and prostatic cancer series of rates in each cohort after linear trend effects were removed. The estimated lag period was the same as for the original data.

Spectral analysis gave an estimated lag period of 42 years and a coherence coefficient γ (f) of 0.990 between gonorrhea input series and prostatic cancer output series providing evidence that the true coherence coefficient differed from zero at level $p < .05$ when tested using tables in Amos and Koopmans[11] (7)

Based on the fact that incidence of cancer of the prostate has been on the rise until the present, one could argue that the drop in mortality from cancer of the prostate after 1965 is due to improvements of medical and surgical management of the disease and thus the declining limb of the curve in figure 5 is coincidental and has nothing to do with gonorrhea incidence 45 years earlier. (8) The study presented

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[5] Trends in death rates for 10-year age groups 40 years and over has not been illustrated for Denmark because recording of mortality from cancer of the prostate by age in that country started as late as 1950 and the number of deaths in age group 40-49 were too few (ranged between 2 and 6 annually).

[6] Average rates of each two successive years were used to smoothen fluctuations of rates from year to year.

[7] The fundamental frequency was estimated at .045 cycles/year for both series. A maximum of 10 years was used to estimate the lag period.

[8] Incidence of prostatic cancer in the U.S., as in Denmark, has been on the rise in the past 3 decades. However, mortality rates showed constant increase from 1937-1956 and has been declining since.

in this paper, being of the observational type, cannot give absolute evidence to refute this argument. However, the following points are against the coincidental theory:

1. The disparity between incidence and mortality after 1965 does not disprove the hypothesis made in this paper, because persistent increase in incidence of prostatic cancer could be attributed to many factors other than increased exposure or susceptibility to carcinogenic agents with time. The increase may be incidental to improvement in survey techniques, changes in medical care delivery to elderly individuals who might have gone undiagnosed, wider use of prostatic resection for urological symptoms that may now more safely be performed with the elderly and the greater use of pathological examinations of surgical specimens from prostatic resections.

2. The good fit between the curves of gonorrhea incidence and prostatic cancer mortality rates for a period as long as 30 years makes the coincidental explanation unlikely.

3. Improvements in medical care and increased survival while a plausible explanation for the recent downward trend in mortality from prostatic cancer in Denmark, cannot possibly account for the sudden reversal of mortality trends from a persistent increase for over 25 years (1941 to 1965) to a continuing decline afterwards. In fact, mortality rates declined by 24.3% in this five-year period. There has been no breakthrough in medical or surgical management of prostatic cancer after 1965 to account for this dramatic change.

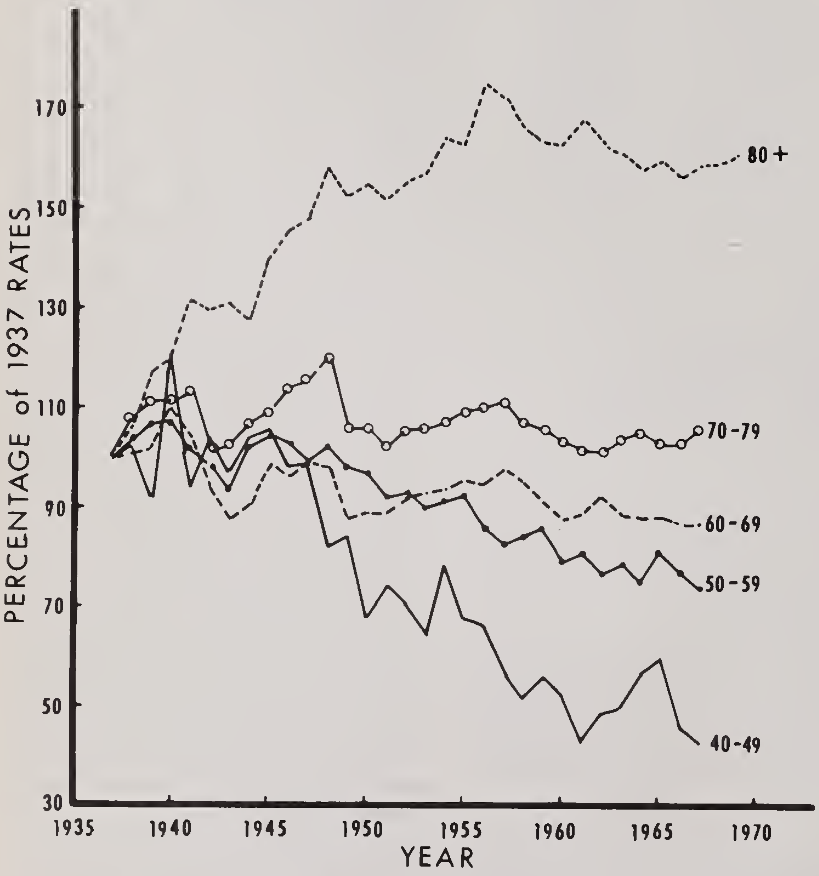

Fig. 3. Percentage of 1937 age specific death rates from cancer of the prostate, per 100,000 males, U.S.A. 1937-1967.

The authors wish to emphasize that neither a good fit of gonorrhea incidence and cancer mortality curves nor a high coherence between rates prove a cause-and-effect relationship between the two diseases. This study merely indicates that there is a relationship between a series of pre-chemotherapy gonorrhea incidence rates and prostate cancer death rates which suggest that there may also be relationship between contracting gonorrhea before the advent of sulfonamides and penicillin, and development of cancer of the prostate gland later in life.

If this relationship is of causal nature, and the iatrogenic complications of pre-chemotherapy management of gonorrhea is one of the etiologic factors of prostatic cancer, we could predict a continuing decline of mortality from this disease due to the attrition. of the cohort that received the old treatment.

It is hoped that this paper would bring about interest in conducting retrospective and possibly prospective investigations to study this issue further.

Acknowledgments

The authors wish to acknowledge with gratitude the meticulous work of the staff of the Statistical Division of the National Health Service of Denmark in compiling the needed data. Special thanks to Mr. Henry Hamtoft, and Mrs. Erna Frandsen for their cooperation and prompt response to our request. In addition, we wish to acknowledge Ms. Catherine Connally and Diane Washington for their valuable assistance in computation; and Dr. Eugene Harris of NIH for his suggestions regarding time series analysis.

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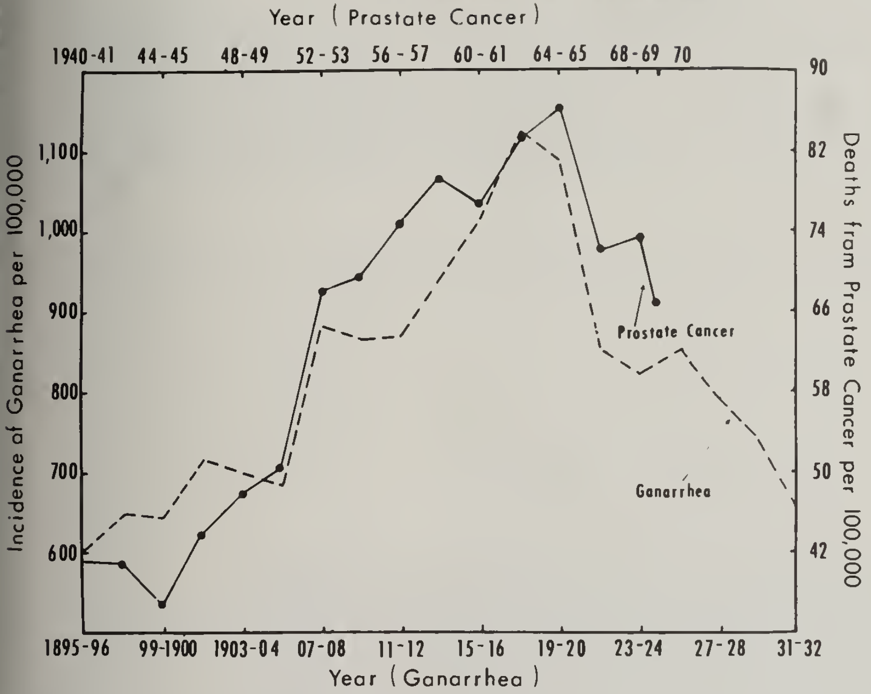

Fig. 4. Two year average incidence rates of gonorrhea, per 100,000 males 15-64 years of age, 1895-1932, and two year average death rates from prostate cancer per 100,000 males 50 years and over, 1940-1970 (Denmark).

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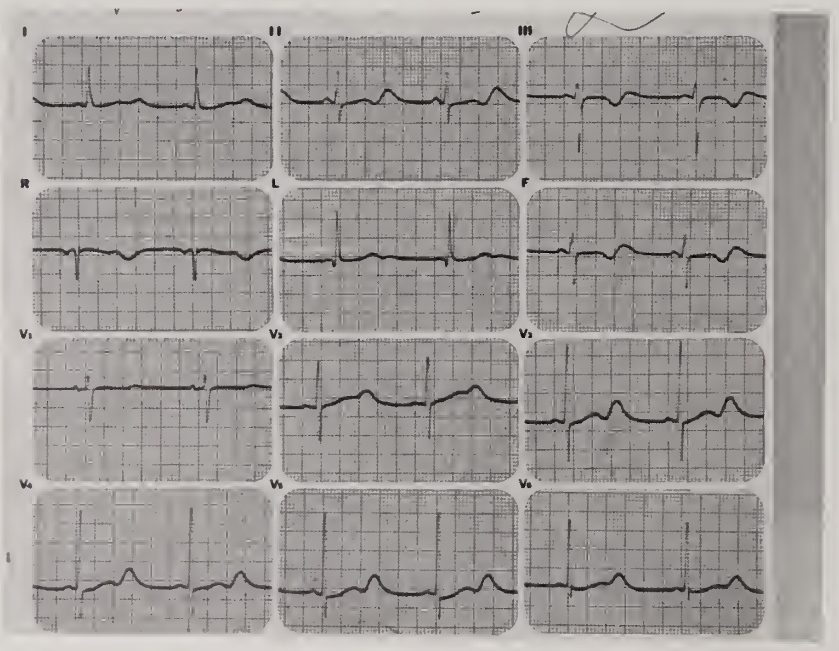
ECG Problems

HISTORY: 59-year-old, Negro female admitted the night before this tracing was taken after an episode of blacking out for a few minutes. She vomited severely, was dyspneic, dizzy, and felt peculiar. A similar episode one year previously was diagnosed as "flu." Some exertional dyspnea, occasional headache, high blood pressure for three years or more. Takes one high blood pressure pill daily.



(for diagnosis see page 392)

Psychological Problems in the Care of the Institutionalized Aged: A Look at D.C. Village*

PAUL R. ROBBINS, Ph.D.† JACK KLEH, M.D.‡ AND HERMAN A. MEYERSBURG, M.D.§

Introduction

A number of writers (Goldfarb, 1953; Meerloo, 1955) have suggested that the care of the aged should include attention to psychological problems as well as physical problems. Nursing homes for the aged, however, are not usually staffed with psychiatrists and some alternative means of coping with psychological difficulties must be found. Various approaches have been tried including individual psychotherapy with aged patients (Goldfarb and Sheps, 1954) group therapy with elderly psychiatric patients (Gunn, 1968; Wolff, 1957), the use of psychiatric consultation with problems of the elderly (Zimberg, 1971) and attempts to introduce broad programs of psychiatric intervention into nursing homes (Stotsky, 1967). While these efforts have met with some success, we are obviously a long way from providing a solution to the problem. In planning programs for the aged, we need to know more about the nature and scope of the psychological problems within nursing homes, the effectiveness of various therapeutic approaches, and how presently available personnel can be best utilized to deal with psychological difficulties. This paper will look at some of these problems as they apply to D.C. Village, a large public institution for the aged in Washington D.C.

D.C. Village, the public residence home for the elderly of Washington, D.C., is administered by the city government. At the time of the study, it had a population of some 800 patients, ranging in disability from some restriction to near total. The patients generally came from low income or indigent backgrounds. The majority of patients were over 75 years in age and 58% of the census was black. The care taking staff included six physicians, 88 nurses, and over 200 attendants. There was no psychiatrist or psychologist on the staff.

In our examination of the institution we focused on four questions: (1) What were some of the psychological factors that seemed to relate to the patients' progress at the village? (2) What was the incidence of noticeable psychological difficulties at the institution? (3) What was the response of the staff to these psychological problems? (4) Would a program of psychiatric consultation be of value in coping with these problems?

Psychological Factors Relating to Patient Programs

To identify some of the psychological factors that might relate to patient progress, we drew on the judgement of the nursing staff. Thirty-two graduate nurses at D.C. Village were given a questionnaire which asked them to think of two of their patients of the same sex and about the same level of physical disability—on who was progressing well and one who was not. A patient defined as showing good progress was one who had improved his ability for self care within the institution or who could be discharged to the community. The nurses were asked a series of questions about each of the patients. The first question was simply to describe the patients briefly, with the nursing responses indicating that 20 of the 32 progressing patients were described in terms such as friendly, pleasant, and cooperative.[1] For example, a female patient, "... quiet, outgoing, takes interest in other patients, friendly, pleasant, appreciates

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* The major portion of these data were obtained in 1971 while Dr. Kleh was chief of Professional Services at D.C. Village in Washington, D.C.

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[1] Two analysts made these classifications independently with 92% agreement.

attention, enjoys helping on unit, sense of humor, keeps herself tidy and clean, enjoys bathing." In contrast, only six of the non-progressing patients were described in such terms. The difference is statistically significant.

The non-progressing patients were described in a variety of ways. A number of these patients seemed to have serious emotional disturbances. For example, "A short, thin woman who, when not kept in a geriatric chair, wanders off of the unit. She is nervous and often pulls off her clothes. She is confused at times . . . She is nervous and nearly always fidgeting." Other non-progressing patients were described as uncooperative and having difficulties with the staff. "Mrs. B. is a very demanding, uncooperative patient . . . She needs assistance in ambulating, self-care; but she usually refuses offer of aid." A few non-progressing patients were described as very dependent.

The suggestion from these data is that the progressing patients were getting along with the other patients and the staff, while the non-progressing patients were not. This impression was confirmed by the responses to a second question asking directly "How does she (the patient) get along with the other patients? In nearly all cases, the answer for the progressing patient was "very well" or "fairly well." For the majority of the non-progressing patients, interpersonal relationships appeared to be disturbed. They were described in such terms as "very shy, keeps to self," "shows no interest, withdrawn," "He doesn't attempt to socialize," "very argumentative, usually clashes with other patients."

The nurses were next asked to rate the patients' usual mood, using a nine-item adjective check list. The adjectives presented were angry, bossy, cheerful, friendly, helpful, irritable, shy, suspicious, and tense. There were a number of differences between progressing and non-progressing patients. The progressing patients were described significantly more often as cheerful and friendly while the non-progressing patients were significantly more often described as suspicious and tense.

The nurses were asked to assess the morale of the patients on a four-point scale (very good, good, fair, poor). In 26 of the 32 cases, the morale of the progressing patient was rated as *higher* than thy paired non-progressing patient.[1] Supporting this finding was the response to the question asking how frequently the patient was depressed. Thirteen of the non-progressing patients were described as depressed "most of the time" or "fairly often" as against two of the progressing patients. Both of these findings are statistically significant.

These data suggested that psychological difficulties in the patients seemed related to their progress at the geriatric center. Further, these psychological difficulties, which included such characteristics as depression, withdrawal, tension, and aggression, appeared to be of a serious order and were reflected in disturbed interpersonal relationships and poor morale.

Dimensions of the Psychological Problem at the Institution

What was the incidence of such psychological problems at the geriatric center? To obtain an estimate of this, an observational study of both medical and psychological problems was carried out on a sample of 144 patients selected randomly from the census at D.C. Village. Each patient was observed for a period of six weeks by the attending nursing staff. The nurses were given a list of symptoms and complaints and asked to record these when they occurred for the patient. Along with a list of physical symptoms, four categories of psychological problems were included: "Noticeably tense or anxious", "noticeably depressed", "noticeably aggressive or abusive", and "noticeably withdrawn". The nurses were also asked to record what response they made to the problem observed, using a precoded system. The major categories of response were:

Listened to problem, no further action seemed needed.
Spent a fair amount of time talking with patient about problem.
Patient given medication (these were further specified) under standing orders.
Patient seen by M.D. on routine rounds.
Attempted to contact M.D.
Other (general nursing) services.

Sixty-eight of the 144 patients or 47% were reported by the nurses to have manifested some noticeable psychological difficulty on at least one calendar day during the observational period. Looking at these 68 patients in terms of the number of days on which they exhibited such difficulties, the distribution appeared skewed with about half of the patients showing only one instance of problems. However, there were a number of patients observed with frequent psychological difficulties. Eighteen percent of the patients were observed with noticeable psychological problems on seven or more occasions. A breakdown of the types of psychological difficulties reported by the nurses indicated that the most frequently observed symptom was being noticeably tense or anxious. This occurred in about 23% of the total sample. Depression, withdrawn behavior and aggressiveness were observed with about the same frequency (about 15% of the total sample).

A question that arises is what was it that the nurses were checking when they reported psychological difficulties? Were these minor problems or major ones? We decided to obtain a first-hand assessment of some of the patients who were frequently observed as manifesting psychological difficulties. A sample of these high frequency cases were examined in psychiatric interviews. Almost all of the patients seen had serious psychological difficulties; some were indistinguishable from those in mental hospitals. For example, one patient had been in a mental hospital for over 30 years before transfer to D.C. Village and was diagnosed as a chronic schizophrenic. During the interview, he put on an impromptu performance of singing and tap dancing. A second patient was extremely suspicious during the interview. She also reported having visions and seemed convinced there was something moving around in her stomach. A third patient was completely withdrawn and uncommunicative during the interview.

The age of the patients did not appear to be an important factor in the presence or absence of psychological symptoms. Patients with psychological complaints were about the same median age as those without such symptoms. Interestingly, though, age appeared to play a role in the kind of psychological symptoms manifested. The younger patients showed a somewhat higher tendency to be depressed while the older patients were reported as more aggressive. The very oldest patients seemed particularly aggressive.

Response of Staff to Psychological Difficulties

There was little tendency for physicians to become directly involved in coping with the psychological difficulties of the patients. There were only two such instances reported during the six weeks observational period. The nursing staff handled these problems when they arose.

Using the precoded response scheme, the nurses most frequently responded to psychological symptoms by talking with the patient about his problem (81 total instances) or by providing some kind of general nursing service, also 81 instances. A decision that no further action seemed needed was made in 66 instances. The use of psychotropic drugs was noted in only 20 instances, most frequently in response to manifestations of tension and aggression.

An interesting difference was observed in the response of the nursing staff to psychological problems when they occurred in patients who also had been showing physical complaints. When patients exhibited both kinds of problems, nurses were significantly more likely to respond by listening to the problem and taking no further action than when patients exhibited psychological problems alone.

Evaluation of a Psychiatric Consultation Service

With the apparent need for psychiatric services at the geriatric center and the lack of a psychiatrist on the staff, an attempt was made to introduce a program of psychiatric consultation into the geriatric setting. The consultations were held twice a month. Usually, patients were selected by the medical staff for review. For the most part the patients had psychological or neurological problems as well as serious medical difficulties. Some of the patients were in very poor condition. The attempt was made to get a wide representation of the staff at these meetings: the physician and nursing staff responsible for the patient, physical and occupational therapist, social worker, and attendants who worked with the patient.

The usual format at these sessions was (1) descriptions of the patient's background, behavior and personality by staff members (2) psychiatric interview of the patient (3) neurological examination if required (4) general discussion and (5) recommendations by the consulting psychiatrist.

After 36 patients had been seen, an attempt was made to evaluate the service on two levels: impact on the participating staff and effects on the patients seen. To assess staff reactions, a short questionnaire was filled out anonymously by twenty of the persons who attended the sessions. Briefly, these data indicated that this type of consultation was seen as having some value, but was well short of what was needed for staff development. For example, when we asked "Have you come away from these sessions with any new understanding or insights?" and if *Yes* "please explain briefly," only eight of the 20 respondents said "Yes". Or when we asked "Did these sessions change your view of any patient you have been caring for in any way?" only six of the 20 respondents said "Yes" and furnished us with examples.

In assessing the effects of the consultations on the patients seen, we used nurses' evaluations routinely collected on all patients at the institution. The ratings made by several nurses on a four-point scale, evaluated the patient's walking, feeding, dressing, bathing, continence, mental state, and behavior. Patients' records were examined for a period of three months[2] before the consultations and three months after. For each category, patients were considered improved (average rating by the several nurses change; in a positive direction), deteriorated (average rating changed in a negative direction), or not changed.

Of the 36 patients seen in the consultations, nine were recent admissions to the home and no nursing evaluations were made prior to the consultations. Seven of the 27 patients for whom data were available, died during the short follow-up period. For the 20 remaining patients, the data indicated little improvement. Five of the patients showed a pattern of improvement (more positive changes than negative ones among the seven categories used), four showed a pattern of no net change while 11 showed an overall pattern of deterioration. This would mean that only 5 of 27 patients showed a pattern of improvement in the three months after the consultation.

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[2] On a few cases, there were records on only one or two months before the consultation, and preconsultation judgements were based on these.

Discussion

The initial study of nurses' perceptions of progressing and non-progressing patients confirms previous reports (Gelfand, 1968: Dominick, et al, 1968) that social-psychological factors are important in the patient's response to the geriatric institution. In interpreting these data, however, one can not determine the extent to which the psychological factors were causes of patient progress or were the effects of such progress. Further research on this question seems needed. We also need to know more about why some patients are able to make a satisfactory adjustment to institutionalization in the nursing home while others are not.

The six week observational survey utilizing the nursing staff appears to be a potentially useful way of obtaining data about what is going on in a large institution. Our data on the validity of this self-survey, however, are limited. Some of the patients reported by the nurses as showing frequent psychological problems were seen in psychiatric interviews and found to be much as the nurses described. Still, more systematic data about both the reliability and validity of this technique is obviously needed. To the extent we can gauge the situation from the present data, the survey suggested that psychological difficulties occurred in a fairly large percentage of the patients (nearly half) on an occasional basis, with a subsample of about one patient in ten showing repeated problems. These data support previous reports (Goldfarb, 1953) which indicate the need for some means to provide psychiatric services for elderly patients.

The survey indicated that it is the nursing staff rather than the physicians who by and large make the response to psychological difficulties when they do arise. If this situation continues to hold, the focus for improving psychological care of the patients, therefore, would seem to be on the nursing and attendant staff. The survey data suggest that of the response alternatives presented, the nurses tended to make three kinds of response to psychological difficulties: attempt to talk with the patient, provide a nursing service, or listen and make a judgment that no further action on their part is needed. To the extent that this latter response means ignoring the patient, it seems a missed opportunity to provide therapeutic contact. The patient is indicating some kind of need when anxious, aggressive, or depressed, and avoiding him is not likely to solve the problem. That nurses appear more likely to do this to patients who show both physical and psychological complaints suggests that nurses may perceive such individuals as "crocks"; patients with a host of problems, not easily treated and perhaps not real—patients to be avoided. In any event, the first approach—talking with the patient—would seem the one to be stressed. The question arises as to how to maximize the therapeutic value of the nurse when she responds to a psychological problem of the patient, as many nurses and attendants are not adequately trained for this.

In-service education about psychiatric problems and the way to respond to them would seem to be a possible solution. In our study, we explored the possibility of providing education in the context of psychiatric consultation about specific patients. Evaluation of this service indicated that the effects on the staff were modest. Only a few participants could specify changes in their behavior toward patients in the weeks following these sessions. Perhaps consultation sessions oriented to specific problems the nurses themselves bring up might have greater value. As such consultation appears to be of limited value, by itself, it seems desirable to integrate it with other kinds of educational procedures in a broad program of continuing nursing education.

The effects of the consultations on the patients were not encouraging. Most of the patients seemed to deteriorate after the meetings and a number died. As many of these patients seen in the consultations were in poor condition, the odds for success were not high. While a control group was not used for comparison purposes, the high incidence of deterioration suggests that if psychiatric consultation is to be used profitably in a geriatric setting, screening is essential to select patients medically sound enough to have a reasonable change of profiting from attention to their psychological problems. Such consultation could be held shortly after the patient's admission and used in the overall planning of his care.

Acknowledgments

The authors would like to acknowledge the assistance of Elizabeth Young, Don Hall and Ruth Wise in carrying out the study. Special thanks are due to M. Madaline Kuhar and the nursing staff of D.C. Village for their cooperation.

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A Case of Severe Varicella in an Adult

**HABIB O. FARHOUDI, M.D.*, VINOD R. MODY, M.B.B.S., F.R.C.P.E., D.T.M. & H.†
AND COROLYNNE G. BRANSON, M.D.§**

Varicella in adults is often serious and often is presented in an atypical form. The following is a case of severe and atypical varicella with our recommendations for diagnosis in doubtful cases, such as this one.

Case History

A 27 year old black male was admitted April 3, 1972 to D.C. General Hospital with the chief complaint of pruritic rash, back pain, fever and shortness of breath. Six days prior to admission he noticed a few "bumps" on the back of his hands and felt feverish. The following day he started experiencing severe low back pain, weakness and felt more "feverish". The rash then involved his forearams and face. He was seen in the emergency room of another hospital, given the diagnosis of measles, an injection of gamma globulin, and an expectorant. Three days prior to admission the rash covered his entire body. At this time he also noted black stools. He was admitted, after a chest x-ray in the emergency room showed a bilateral diffuse nodular infiltrate. The patient gave no history of foreign travel. He had been vaccinated as a child and by the Army, with no reaction. He had had indirect contact with a case of varicella two weeks prior to the onset of his illness.

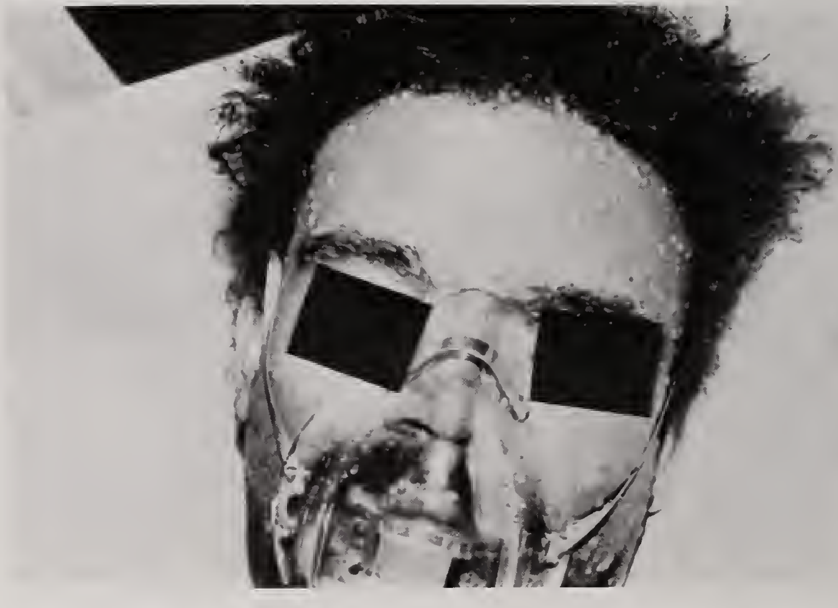

FIG. 1. Extensive involvement of head and neck by varicellar rash. Rashes appear almost all at the same stage.

Physical examination on admission showed a well developed, well nourished, but very sick young man toxic in acute respiratory distress. His blood pressure was 120/70, his pulse 100, and his temperature 100°F. The rash covered his entire body and was most marked on the face and trunk was papulo-vesicular, in varying stages of development, with central umbilication and a few scabs. The lesions were variable in size from 2 to 6 mm, and a few lesions felt shotty. There were lesions on his palms and soles, scalp, and in the mouth (especially on the soft palate). There was no vaccination scar. Auscultation of the lungs revealed moist rales bilaterally, particularly at the bases. The stool was hematest positive. The remainder of the physical examination was unremarkable.

Laboratory Data

The white blood count on admission

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was 8.4×10^3 with repeated counts of 6.3×10^3, 7.5×10^3 and 11.5×10^3. Hematocrits were 47.6%, 46.0%, and 44.9%. The serum glutomic oraloacetic transaminase was 52 and 38 units, and the lactic acid dehydrogenase 1320 and 490 units. Blood urea nitrogen, glucose, electrolytes and arterial blood gases were within normal limits.

Hospital Course

During the first few days of hospitalization, the patient had significant respiratory distress and needed oxygen by mask constantly. On the third hospital day his skin lesions began to dry and the lesions in his mouth began to heal. He continued to improve and was discharged April 13, 1972 with marked scarring still present.

Discussion

In typical cases of varicella the eruption, as a rule, appears first on the back or chest, following two to three days of malaise and/or low grade fever. Typically the lesions appear in crops and rapidly a papule becomes a vesicle and then a crust; therefore, all three stages may be seen side by side. Histologically varicella lesions consist of intraepidermal vesiculation characterized by reticular and ballooning degeneration with vesicle formation. The vesicles are usually superficial and therefore easily rupture when they occur in normal skin.

In adults varicella is more severe and is at times atypical. In florid cases the rash may simulate smallpox eruption, especially when there is extensive involvement of head, neck (Fig. 1) and extremities. In these cases mucosal involvement is not infrequent. Hemorrhagic tendencies, thrombocytopenia, purpura fulminans and hemorrhagic chickenpox have been reported [1-4]. There have also been reports of hematuria[5] and bleeding from the oral cavity[6] as a result of mucosal lesions. In severe cases the lesions may appear in the esophagus, lungs, pancreas, liver, kidney, bladder, ureter and adrenal glands[7].

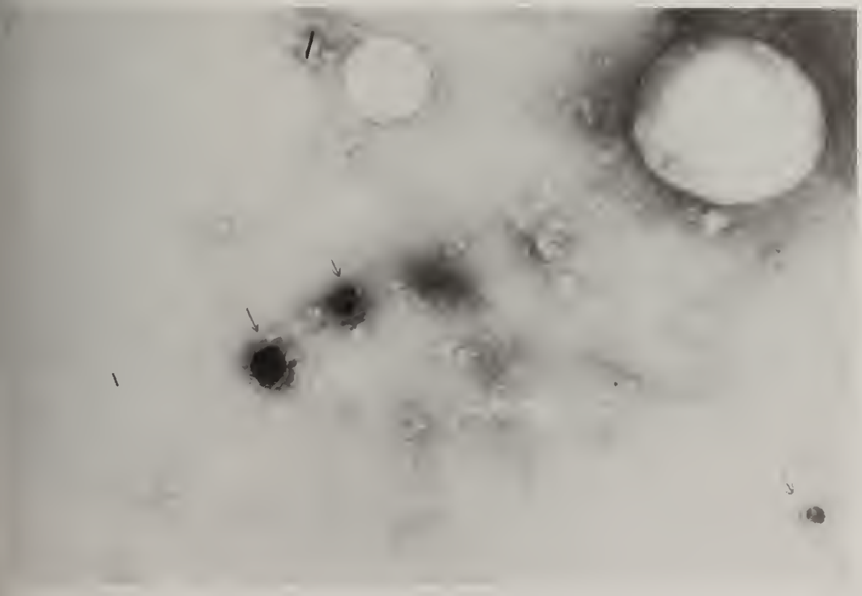

FIG. 2. Electron miscroscopy of vesicular fluid, Viral particles have been identified by arrows.

There is no difficulty in differentiation of varicella from smallpox in typical cases. However, in florid and atypical cases such as our case, the differentiation may become quite difficult and special laboratory procedures may be required. It is probable that many florid cases of smallpox may be misdiagnosed as a case of smallpox, in smallpox endemic areas. In such cases the final diagnosis is based on the demonstration of multinucleated giant cells in vesicular fluid and scrapings from varicella lesions, or by electron microscopic examination which reveals viral particles in vesicular fluid (Fig. 2). In questionable cases it is advisable to seek help from the Public Health Department or directly from Communicable Disease Control (C.D.C.), Atlanta, Georgia, for confirmation of the diagnosis. In our case we were able to receive confirmation of diagnosis by electron microscopic examination from C.D.C. within 24 hours.

Acknowledgments

We wish to thank Dr. Thomas Day and Dr. Robert Marier for their invaluable help in collection of vesicular fluid.

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ECG Diagnosis

INTERPRETATION:
1. Sinus bradycardia.
2. ST-T changes consistent with ischemia and low serum potassium.
3. Giant U waves suggest hypokalemia.

The heart rate is 54 per minute with a P wave preceding each QRS complex and a PR interval of 0.14 seconds. The QRS interval is 0.06 seconds. The frontal plane electrical axis is approximately $-15°$.

The most significant abnormalities involve the ST-T and U portions of this electrocardiogram. The T waves are inverted in leads II, III and aVF. In the other leads, they are upright, though fairly low. The terminal portion of the T wave is masked by the enormous U waves. These are best seen in leads V_2-V_6. Such gigantic U waves are uncommon, and represent an exaggeration of the abnormal U waves usually seen in hypokalemia.

This patient's serum potassium was 2.5 mEq. per liter. The blood pressure medicine she was taking proved to be a diuretic. Simple replacement of the potassium led to prompt improvement with return of the electrocardiogram to a completely normal tracing, though with sinus bradycardia the following day.

Edited by Robert R. Montgomery, M.D.

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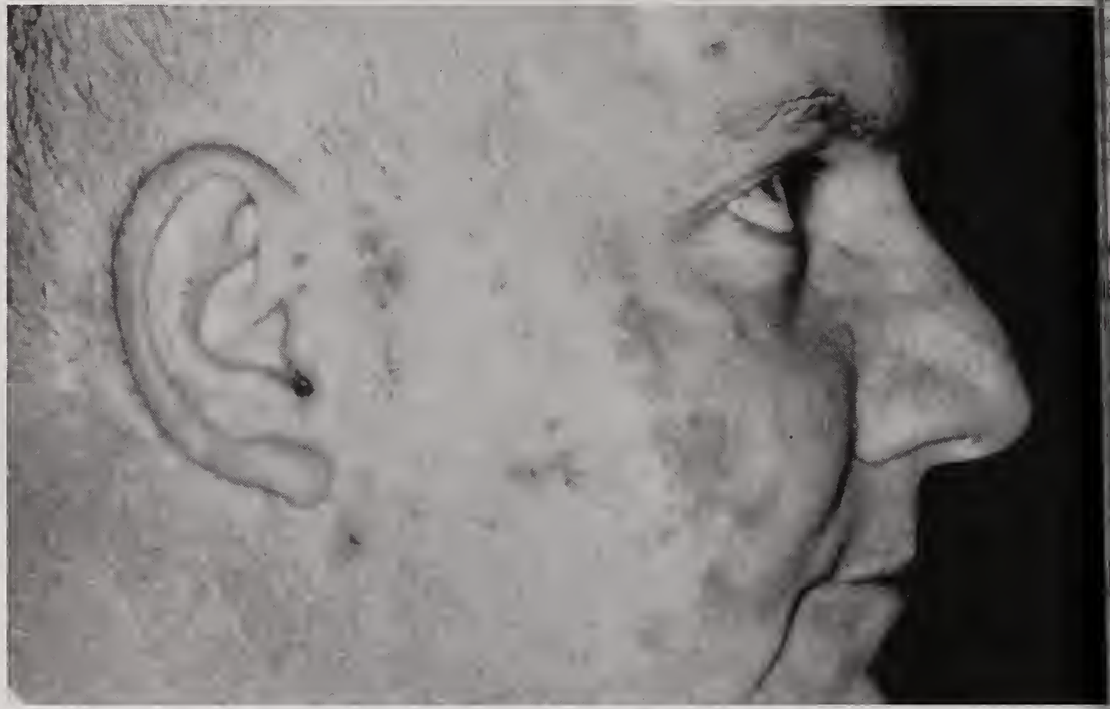
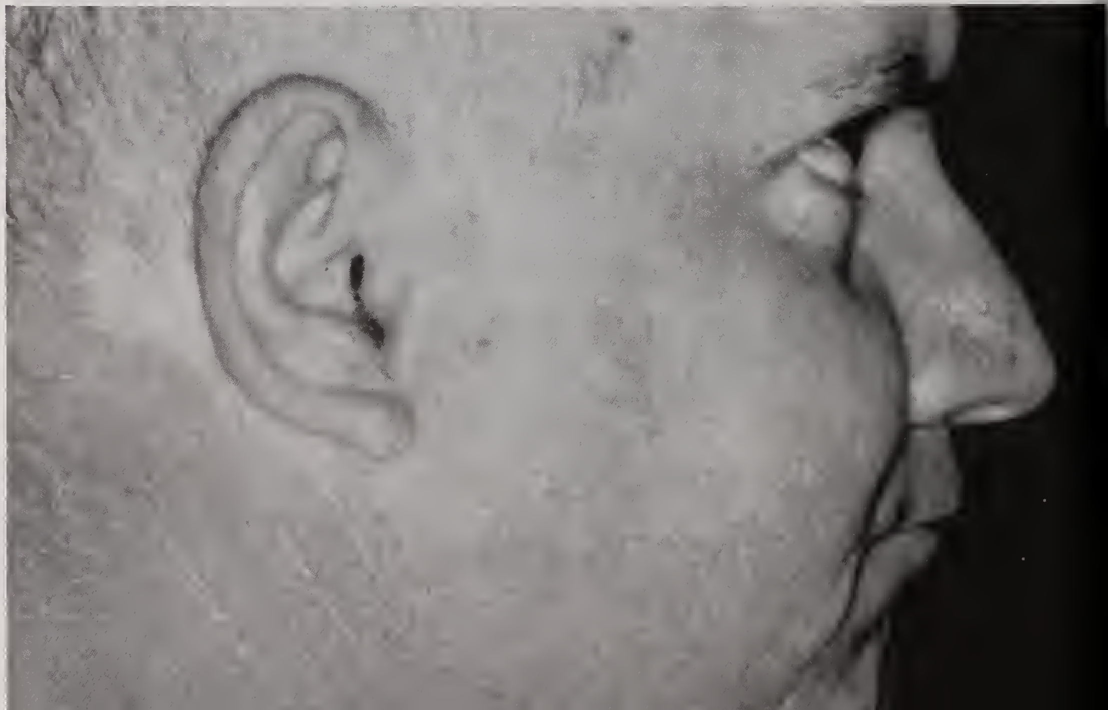
Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.



Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.



*Data on file, Hoffmann-La Roche Inc., Nutley, N.J

he lesions on his face
re solar/actinic–
o-called "senile" keratoses...
nd they may be premalignant.

lar, actinic or senile keratoses

se lesions may be called by several names, but they
ally can be identified by the following characteris-
. The typical lesion is flat or slightly elevated, of a
wnish or reddish color, papular, dry, rough, adherent
sharply defined. They commonly occur as multiple
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quence of therapy–
lectivity of response

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thema may begin to appear in the area of the lesions;
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Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

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THE VIEW BOX

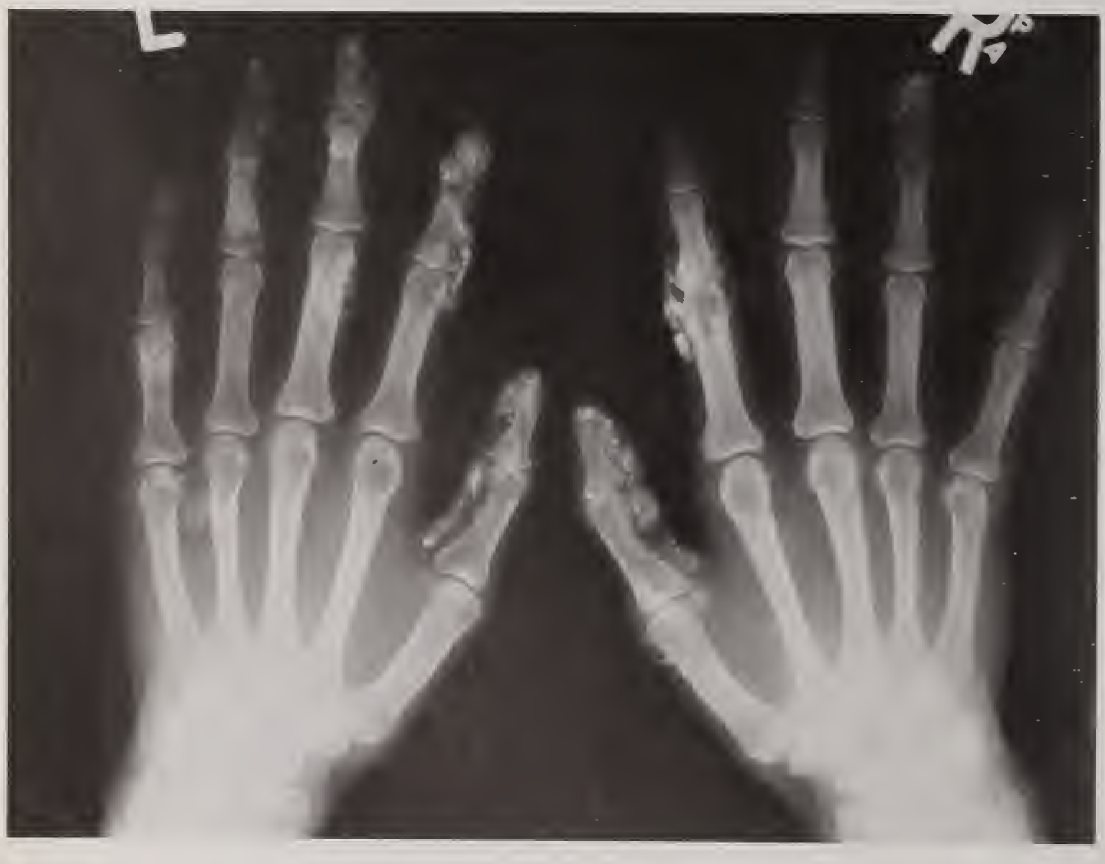
Prepared By
The Department of Radiology
Washington Hospital Center

A middle aged housewife with complaints of stiffness and tightness in her hands. Clinically a Raynaud's phenomenon was present.

DIAGNOSIS: Progressive systemic sclerosis (Scleroderma)

NOTE: Amorphous calcifications in the subcutaneous tissues and the resorption of soft tissue about the tips of the 1st and 2nd digits.

Soft tissue calcification occurs in a variety of systemic diseases, hyper vitaminosis D, hypo and pseudohypoparathyroidisim and by contrast to these rare entities most commonly in progressive systemic sclerosis. This patient had involvement of the gastrointestinal tract (esophagus and colon) by the disease and clinically the possibility of CRST syndrome existed (a variation of scleroderma).



CRST = calcifications, Raynaud's, sclerodactyly and telangiectasia.

In the CRST syndrome the calcifications occur most often in the joint capsules and tendons rather than the soft tissues.

Edited by Gunther J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

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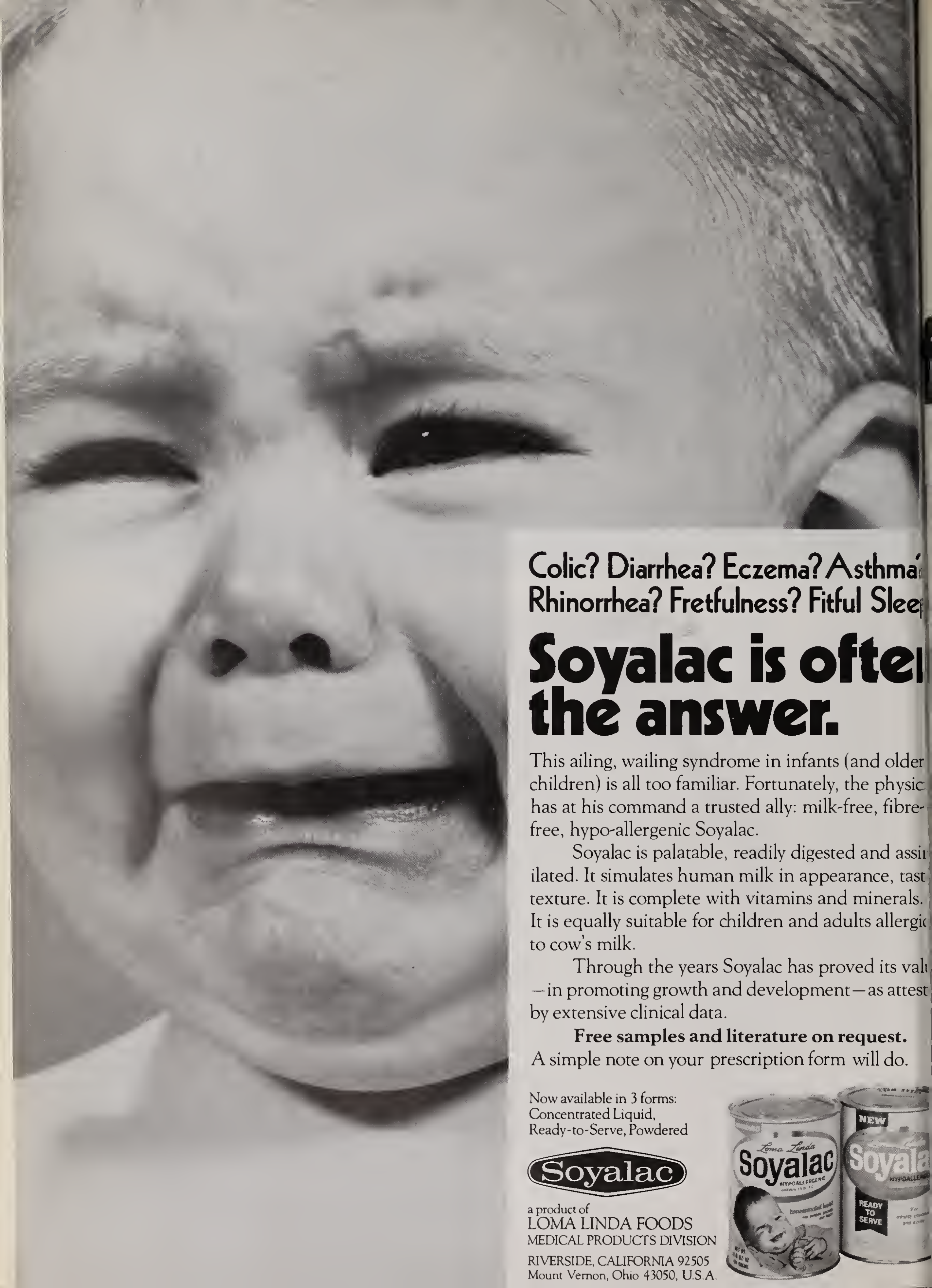

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Indications: For the treatment of trichomoniasis in both male and female patients and in the sexual partners of patients with a recurrence of the infection provided trichomonads have been demonstrated by wet smear or culture. The oral tablets are indicated also for acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a history of hypersensitivity to metronidazole.

Warnings: Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn.

Precautions: Mild leukopenia has been reported during its administration; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, vomiting and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry or sore tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Monilia,* exacerbation of vaginal moniliasis, an occasional reversible moderate leukopenia, dizziness, vertigo, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, mouth, vagina or vulva, pruritus, dysu cystitis, a sense of pelvic pressure, dyspareu fever, polyuria, incontinence, decrease libido, nasal congestion, proctitis, pyuria darkened urine have occurred in patients ceiving the drug. Patients receiving Fla may experience abdominal distress, nau vomiting or headache if alcoholic bevera are consumed. The taste of alcoholic bev ages may also be modified. Flattening of T wave may be seen in ECG tracings.

Dosage and Administration: For Tric moniasis. *In the female:* One 250-mg. tab orally three times daily for ten days. Cour may be repeated if required in especially st born cases; in such patients an interval of f to six weeks between courses and total and ferential leukocyte counts before, during, a after treatment are recommended. Vaginal serts of 500 mg. are available for use, parti larly in stubborn cases. *When the vaginal*

the vaginal vault each day for ten days and
ne oral dosage is reduced to two 250-mg. tab-
ts daily during the ten-day course of treat-
ent. Do not use the vaginal inserts as the sole
rm of therapy. *In the male:* Prescribe Flagyl
nly when trichomonads are demonstrated in
ne urogenital tract, one 250-mg. tablet two
mes daily for ten days. Flagyl should be taken
y both partners over the same ten-day period
hen it is prescribed for the male in conjunc-
on with the treatment of his female partner.

or Amebiasis. *Adults:* For acute intestinal
mebiasis, 750 mg. orally three times daily
or 5 to 10 days. For amebic liver abscess, 500
o 750 mg. orally three times daily for 5 to 10
lays. *Children:* 35 to 50 mg./kg. of body
veight/24 hours, divided into three doses,
rally for ten days.

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References:

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FRIDAY, OCTOBER 12, 1973

CURRENT CONCEPTS IN CORONARY ARTERY DISEASE

Moderator—Herbert L. Tanenbaum, M.D.

9:00 a.m. Welcome—Irving Burka, M.D.
President, Medical Society of D.C.

9:15 a.m. Pathophysiology of Ischemic Heart Disease
Richard Gorlin, M.D.
Chief, Cardiovascular Division
Peter Bent Brigham Hospital

10:00 a.m. Clinical—Hemodynamic Correlations in Coronary Artery Disease
James J. Morris, Jr., M.D.
Associate Professor of Medicine
Director, Myocardial Infarction Research Unit
Duke University Medical Center

11:00 a.m. The Surgical Treatment for Ischemic Heart Disease
Floyd D. Loop, M.D.
Surgeon, Department of Cardiovascular Surgery
The Cleveland Clinic Foundation

11:45 a.m. Panel Discussion

CURRENT TRENDS IN THE MANAGEMENT OF GASTROINTESTINAL HEMORRHAGE

Moderator—Stuart H. Danovitch, M.D.

2:00 p.m. The Radiologists' Role in Gastrointestinal Bleeding: Diagnostician and Therapist
William B. Seaman, M.D.
Director of Radiology
Columbia-Presbyterian Medical Center

2:30 p.m. Is Gastrointestinal Endoscopy Necessary in Acute Gastrointestinal Hemorrhage?
William I. Wolff, M.D.
Director, Department of Surgery
Beth-Israel Medical Center

3:00 p.m. Newer Therapeutic Endeavors: Gastric Cooling and the Use of a "G-Suit"
Stephen L. Wangensteen, M.D.
Professor of Surgery
University of Virginia Medical Center

3:30 p.m. The Appraisal of Current Diagnostic and Therapeutic Techniques in Gastrointestinal Hemorrhage
Thomas C. Chalmers, M.D.
Associate Director for Clinical Care
Director, The Clinical Center
National Institutes of Health

4:15 p.m. Panel Discussion

SATURDAY, OCTOBER 13, 1973

FUNDAMENTAL PROBLEMS IN INTENSIVE CARE

	Moderator-Burdett S. Dunbar, M.D.
9:00 a.m.	The Intensive Care Unit–Why and When? Robert R. Kirby, M.D. Assistant Professor of Anesthesiology University of Florida
9:30 a.m.	Recognition and Management of Respiratory Failure Joseph M. Civetta, M.D. Associate Professor of Surgery, Anesthesiology and Medicine University of Miami Director, Intensive Care Unit Jackson Memorial Hospital, Miami, Florida
10:00 a.m.	Acute Renal Insufficiency–Causes and Treatment W. Gordon Walker, M.D., Professor of Medicine Director, Division of Nephrology The Johns Hopkins Medical Institutions
10:45 a.m.	Sepsis Kenneth G. Swan, M.D., LTC, MC Director, Division of Surgery Walter Reed Army Medical Center
11:15 a.m.	Psychological Aspects of Intensive Care Units Harry S. Abram, M.D., Professor of Psychiatry Vanderbilt University Medical Center
11:45 a.m.	Panel Discussion

THE PHYSICIANS RESPONSIBILITY IN THE TREATMENT OF TUBERCULOSIS

	Moderator—K. Albert Harden, M.D.
2:00 p.m.	Preventive Treatment of Tuberculosis Phyllis Q. Edwards, M.D. Chief, Tuberculosis Branch State and Community Services Division Center for Disease Control, Atlanta, Georgia
2:15 p.m.	Current Trends in the Medical Treatment of Tuberculosis William Lester, M.D. Professor, Department of Medicine The University of Chicago
2:30 p.m.	Present Status of Surgery in the Management of Pulmonary Tuberculosis W. Glenn Young, Jr., M.D. Professor of Surgery Duke University Medical Center

2:45 p.m. The Community Health Problem of Tuberculosis in the Inner Cities
William C. Banton, II, M.D., M.P.H.
Special Consultant for Health and Hospital Coordination, St. Louis County, Missouri

3:30 p.m. Panel Discussion

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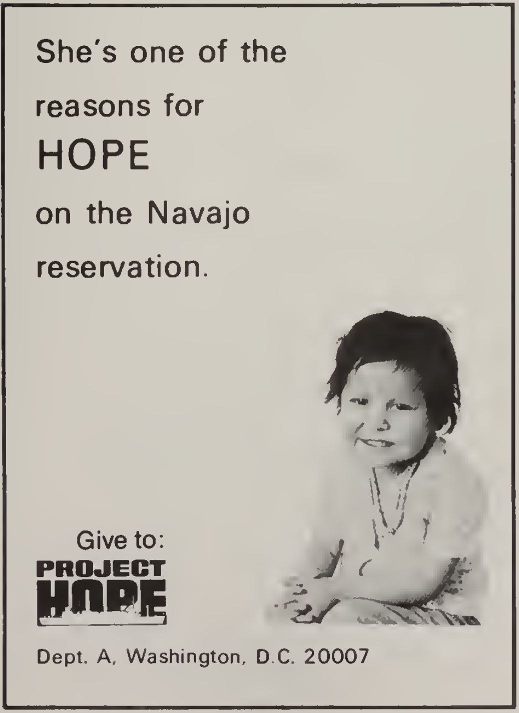

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book REVIEWS

Pathophysiology of Gestation. NICHOLAS S. ASSALI AND CHARLES R. BRINKMAN. Vol. I: Maternal Disorders, Price, $29.00, 617 Pp. with illustrations; Vol. II: Fetal and Placental Disorders, Price, $26.00, 357 Pp. with illustrations; and Vol. III: Fetal and Neonatal Disorders, Price $32.50, 556 Pp. with illustrations. New York: Academic Press, 1972.

In *Pathophysiology of Gestation,* Assali, together with 28 other experts, has accomplished a herculean task abstracting and interrelating pertinent data from an enormous amount of reference material. The presentation differs from conventional texts in that emphasis is placed first on the basic physiology and biochemistry of the mother, placenta, fetus and neonate and, subsequently, on the pathophysiology leading to recognized problems of pregnancy and the neonate. The well-organized format of this three-volume treatise guides the reader through otherwise difficult material. Each chapter follows a standard sequence: a brief index, introduction, well-referenced text, summary, and references. Each volume also concludes with an author and subject index. Though the material is heavily drawn from the work of medical scientists and basic researchers, there is a wealth of clinically valuable material available to those who are willing to abstract it.

The first volume includes seven chapters covering disorders of ovulation, gamete transport, uterine function, maternal circulatory and respiratory adjustments, kidney fluids and electrolytes, liver and lactation. The second volume consists of five chapters covering disorders of placental transfer and endocrine function, amniotic fluid, genetic defects and environmental teratology. The third volume, comprised of eight chapters, includes fetal and neonatal disorders of circulation, respiration, endocrine function, fluid, and electrolytes, nervous system, immunology, hematopoiesis and bilirubin metabolism.

In general, while the three volumes are all very well written, some chapters are outstanding in organization and clarity of presentation (i.e. Vol. I chapter 2, Vol. II chapter I, Vol. III chapters 2 and 7).

Volume I draws heavily from research in multiple animal species, while volumes II and III are drawn more from human research data. Consequently, volume I presents much more complete data on mechanisms of normal and abnormal physiology than can be found in volumes II and particularly volume III. In each chapter, the material presented is a skillful blend from the very detailed complex data important to the basic research scientist to the relatively simple anatomic descriptions that were quickly learned in medical school. Hence there is something of value for a wide range of interested readers.

Volume III attempts, with moderate success, to consider in some detail each of the major problems that could confront the neonate. For more detailed reading, the appropriate references are well cited in the text.

In volume III, chapter 3, sections are presented on management of infants born to diabetic women and treatment of complications. The attempt to summarize the treatment of hypocalcemia and hypoglycemia is at best very confusing should a reader be previously unfamiliar with the subject. It is one of the rare places where any attempt to discuss treatment is made and seems out of context with the general theme of the treatise. These areas should be better referenced and presented with considerably greater clarity.

The entire work is well worthwhile as reference material for those involved in research or teaching in this field.

MILTON W. WERTHMANN, JR., M.D.

Justifying Violence: Attitudes of American Men. BLUMENTHAL, KAHN, ANDREWS & HEAD. Price, $5.50 paperbound and $8.50 clothbound. Pp. 367. Ann Arbor, Michigan: Braun-Brumfield, Inc., 1972.

In the aftermath of the violence that was characterized by the assassinations of President Kennedy and Martin Luther King, the authors have undertaken to study the emotional climate of the United States to ascertain the degree to which violence is condoned or condemned in this country. Their thesis is that the evaluation of such attitudes could serve as barometers to assess the state of a community before catastrophe actually occurs, though they recognize the limits of this essentially sociologic approach.

Violence tended to be defined by the men being studied as something that was not good, legitimate or necessary. Thus, for instance, whether sit-ins and protest demonstrations were considered violence depended on the political views of the person being interviewed.

The study undertakes to explore the attitudes of random samples of American men with regard to the uses of violence to maintain or alter social structure. The findings indicate that at the time of the study (1969), 65% of American men were concerned with violence as it pertained to protest and dissent. While 70 to 80% agreed that social conditions fostered such violence, a large number of those studied felt the solution was to be reached through the use of counter-violence rather than correction of the elements labeled as causal.

The summary of the ability to predict, of the study, concludes that an individual's values, social beliefs, views on violence as a useful or harmful tool and his identification with specific social groups are the major determinants in his justification of violence. "An individual can justify violence more easily when it is used by people who share his goals and is used against those who hold antithetical goals."

Though there has been a great deal of effort expended in the interviews, charts and tables, the conclusions reached by the study hardly seem startling or indicative of hitherto obscure data. For those interested in broad social-psychological issues, some of the statistics assembled may prove interesting. For the majority of psychiatric and medical practitioners, the book has little to recommend, and one is left with the impression that the book was written to justify the study.

EDWARD I. KUSHNER, M.D.

Functional Aids for the Multiply Handicapped. ISABEL P. ROBINAULT, PH.D., Editor, Price, $10.00. Pp. 233. Hagerstown, Maryland: Harper & Row, 1973.

This is a resource book on functional aids, devices and equipment which might be used for many handicapped individuals. However, in the main, it is the type of equipment developed and adapted for the cerebral palsied child. In this, the title is perhaps misleading.

There is little in the book for the handicapped adult and little for any handicap other than cerebral palsy. The book has 300 adequate illustrations of the equipment and is divided into sections according to use as follows: personal care, communication and learning, and recreation. These sections are further subdivided into chapters in a reasonable format. Included at the end is an alphabetized index of information on where the equipment can be purchased.

This book would serve best as a resource reference for the inexperienced physical or occupational therapist, as well as for students in these fields. It has good practical information with little that is new or different. Much of the information can be gleaned from a manufacturer's catalogue and this method has its merits since one can thereby evaluate products from various companies and select those which best serve the need.

Some of the references are old and might not be readily available such as REHABILITATION GAZETTE 1965 and REHABILITATION RECORD 1967. However, overall, there is a place for such a source book, but it is limited. Few physicians or therapists, other than those dealing extensively with cerebral palsy, would find it useful.

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OBITUARIES

Raymond K. Foxwell, M.D.
1891–1973

Dr. Raymond K. Foxwell, a retired psychiatrist who practiced in the District of Columbia for 45 years, died May 6, 1973. He resided at 5000 Fairbanks Avenue, Alexandria, Virginia.

A native of Leonardtown, Md., he received his M.D. degree from the University of Maryland Medical School.

Positions Dr. Foxwell has held include Assistant Superintendent, State Hospital, Cambridge, Maryland; psychiatrist at the Juvenile Psychopathic Institute, Chicago; and 15-year consultant in neuropsychiatry at the Veterans Administration Diagnostic Center.

After World War II, Dr. Foxwell was awarded a certificate of merit by President Truman for voluntary service in the Selective Service system. He also received a Selective Service Medal from Congress.

Dr. Foxwell was a life member of the Medical Society of the District of Columbia and a member of the American Medical Association Advisory Board.

He is survived by his wife, Evelyn, of the home address.

Peter Duus, M.D.
1907–1973

Dr. Peter Duus, general practitioner in the Washington-area, died June 3, 1973. He resided at 6056 Central Avenue, Capitol Heights, Maryland.

Born in Tandslet, Denmark, he received his undergraduate education from the University of Kopenhagen, Denmark and attended medical school at the University of Kopenhagen, Denmark and the University of Heidelberg, Germany. He received his medical degree in 1946. His internship was served at Prince George's General Hospital and he served residencies at the University Clinic in Heidelberg, Germany, clinics in Denmark, and at Prince George's General Hospital.

Dr. Duus was an Associate member of the Medical Society of the District of Columbia, as well as a member of the American Geriatrics Society and the American Medical Association.

He is survived by his wife Dorothy of the home address, and a son, Peter, Jr.

Murray M. Robinson, M.D.

1909–1973

Dr. Murray M. Robinson, a Washington-area dermatologist for the past 34 years, died June 15, 1973. He resided at 4701 Willard Avenue, Chevy Chase, Maryland.

Born in New York, he received his B.A. and M.D. degree from George Washington University. He interned at Gorgas Hospital, Ancon, the Canal Zone and completed his residency at New York Skin and Cancer Hospital. Dr. Robinson was on the staffs of Garfield Hospital in Washington and Johns Hopkins University Hospital in Baltimore, Maryland. He was also a dermatology consultant at Georgetown University and at Howard University and was an instructor in dermatology at Georgetown University School of Medicine.

A colonel in the Army Reserves from 1939-1953, he also served as a medical director captain in the U.S. Public Health Service and as a staff officer surgeon in the Coast Guard.

Dr. Robinson was the recipient of numerous awards including the Fundacion International Eloy Alfaro medal from the president of Panama, the medal of the International Institute of American Ideals and the Meritorious Service medal of the U.S. Public Health Service.

Dr. Robinson was a Special member of the Medical Society of the District of Columbia. In addition, he was a fellow of the American College of Allergists, the American Academy of Compensation Medicine, the Mexican Academy of Dermatology and the Jerusalem Academy of Medicine. He was also an Associate of the American College of Physicians, the American Academy of Dermatology, and a member of the American Society of Investigative Dermatology, the Baltimore-Washington Dermatological Society, and the American Medical Association.

A past president of the D.C. Dermatologic Society, he also held memberships in the Phi Lambda Kappa Medical Society and the Israel Medical Society.

He is survived by his wife, Ethel, of the home; a daughter, Lynne, of Washington; his mother, Mrs. Samuel Simpson, of Miami Beach; and a brother, Jerome, of Baltimore.

Joseph H. Watson, M.D.

1919–1973

Dr. Joseph H. Watson, a practitioner of internal medicine in the Washington-area, died on June 5, 1973. He resided at 4004 W. Underwood Street, Chevy Chase, Maryland.

Born in Long Island, New York, he received his undergraduate degree from the University of Florida, Gainesville, and his medical degree from Hahnemann Medical College, Philadelphia, Pa. He served his internship and residency at Hahnemann Hospital, Philadelphia, Pa. He also was an assistant clinical professor at the George Washington University School of Medicine.

During World War II, Dr. Watson served in the Army Medical Corps and was decorated with an American Theater Ribbon and a World War II medal. He was recalled to active service in the Korean conflict and served in Japan. During this period, he was commended for his research on hemorrhagic fever among the troops.

An active member of the Medical Society of the District of Columbia, Dr. Watson also was a diplomat of the National Board, a member of the American Medical Association, the American College of Cardiology, the U.S. Association of Military Surgeons, the American Institute of Homeopathy, and the Washington Medical Surgical Society.

He is survived by his wife, Marjory, and son, Joseph, of the home address, two daughters, Mrs. Craig Goodrich of Ripon, Wisconsin, and Inez Watson of Cleveland, Ohio, his mother, Rachel Watson, two brothers, Rudolph and Benjamin Watson of Frostproof, Florida, and a grandchild.

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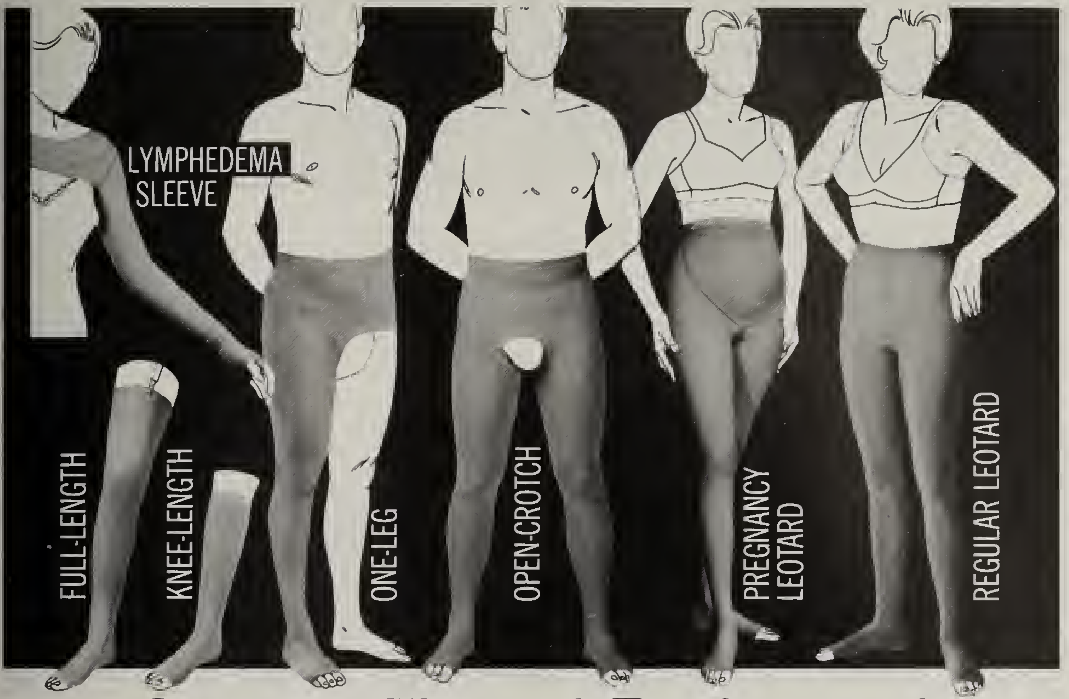
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Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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The by-line, the author's given name and initial or given name alone should be supplied. The M.D. degree or highest academic degree should be listed for each author. Not more than six names should be included as authors, unless the communication is the report of a committee.

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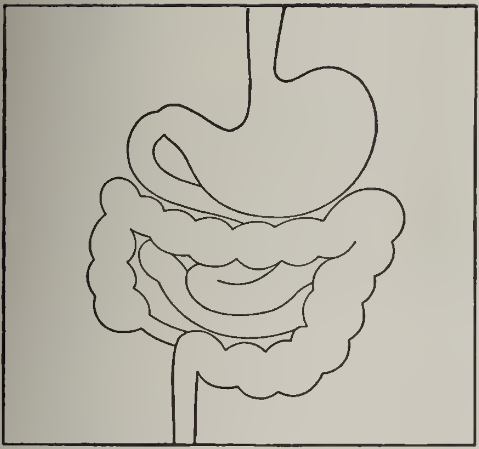

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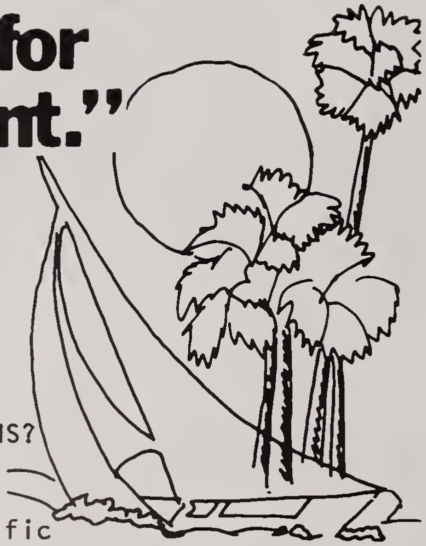

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Geigy Pharmaceuticals 3,
Eli Lilly & Company 6,
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Pharmaceutical Manufacturers Association 4–5
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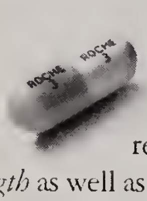

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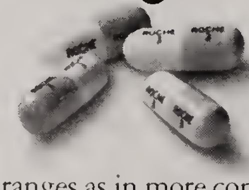

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Precautions: In the elderly and debilita and in children over six, limit to smallest effec tive dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gr ally as needed and tolerated. Not recommende in children under six. Though generally not r ommended, if combination therapy with oth psychotropics seems indicated, carefully cons individual pharmacologic effects, particularly use of potentiating drugs such as MAO inhib and phenothiazines. Observe usual precautio presence of impaired renal or hepatic functio Paradoxical reactions (*e.g.*, excitement, stimul and acute rage) have been reported in psychia patients and hyperactive aggressive children. Employ usual precautions in treatment of an states with evidence of impending depressio suicidal tendencies may be present and prote measures necessary. Variable effects on blood coagulation have been reported very rarely i patients receiving the drug and oral anticoagu lants; causal relationship has not been establis clinically.

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President's Message . . . 1
A Doctors' Union? Irving Burka, M.D.

Editorial 2
The Georgetown University Medical School Issue. John J. Canary, M.D.

SCIENTIFIC ARTICLES

Hypertension and Human Renal Prostaglandins. Vernon K. Vance, M.D. and James B. Lee, M.D. . . . 419

Obesity—A Form of Malnutrition. Malcolm M. Martin, M.D., F.R.C.P. and Arline L. A. Martin, M.A., M.D. 423

Some Thoughts on the Medical Management of Renal Stones. John J. Canary, M.D. 429

Varieties of Hypothyroidism. James A. Pittman, Jr., M.D. 435

OTHER FEATURES

ECG Problems 459

The View Box 422

New Members 461

Book Reviews 463
Acute Inflammation. (Hurley) Reviewed by John Stubenbord, M.D.

Your Brain and Nerve. (Pool) Reviewed by Elliot C. Wilner, M.D.

Understanding Cancer (Brooke) Reviewed by Louis K. Alpert, M.D.

Essentials of Artificial Ventilation of of the Lungs. (Hunter) Reviewed by S. N. Albert, M.D.

The Medical Garden. (Marks and Beatty) Reviewed by Arthur Ruskin, M.D.

(continued)

Obituaries ... 471
David O. Smith, M.D.
Anna Catharine Q. Knop, M.D.
Daniel B. Washington, M.D.
Information for Authors 11–12
Advertising and Subscription Information ... 14
Index to Advertisers ... 14

COMING SEMINARS

Occupational Health Seminar
Medical Society Auditorium
October 25, 1973

Cancer Committee Seminar
Medical Society Auditorium
November 7, 1973

Photo taken at Special Membership Meeting August 1, 1973. Meeting was held to discuss PSRO. Dr. Camalier is shown addressing the meeting. Seated (L to R) are Dr. Ramsey, Dr. Burka and Mr. Ferraraccio.

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PRESIDENT'S MESSAGE

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A Doctors' Union?

Irving Burka, M.D.

This month our country salutes Labor. There is a trend developing in the U.S. to unionize doctors, and it is well to be cognizant of such a trend. It involves a small segment of our profession; however, several unions have, in fact, been activated in different states.

The proponents of unionization strongly feel that in an era of powerful social and economic pressures upon our profession, unionization is the only answer. With such organization, they say, would come strength and unity in negotiating (with government and third party payers) for rights, fees, etc. They point to the great gains of American Labor as a result of unionism since the turn of this century. They claim, therefore, that in unionizing we would become a power in unison with the rest of Labor in this country.

In analyzing the union concept, one concludes that what gives Labor and a union its clout is its capability of strike–the ability to shut down a plant, an industry, and even in the recent past, the Post Office Department of the Federal Government. I admit that this is formidable power, but is this what we want for our profession? Are we, as members of this honorable profession, dedicated to the welfare of a community? Or are we ready to picket, shut down the hospitals and our offices, in order to win material concessions? I believe, without fear of contradiction, that there are but few of us willing to resort to this type of action. Yet, without the will and the power to strike there can be no effective union. It becomes only an economic social club.

The idea of doctors' unions seems demeaning and beneath the dignity of our profession. It isn't unionism we need, but more unity among us. We should strengthen our existing associations and federations of organized medicine; not only for socio-economic reasons, but for the purpose of improving our dedication, education and high standards.

EdiTORiAl

The Georgetown University Medical Center Issue

I am pleased to have participated in the collection of a group of medical papers for the Medical Annals of the District of Columbia. This afforded members of the Georgetown University Medical School's Division of Endocrinology and Metabolic Diseases to publish a few of their studies as a small memorial to the late Doctor Laurence H. Kyle. Doctor Kyle was formerly the Director of this division and then subsequently the Professor and Chairman of the Department of Medicine of the Georgetown University School of Medicine.

I am grateful to the contributors whose papers follow: To Doctor Malcolm Martin who following his training in Great Britain, then at the Harriet Lane Home of the Johns Hopkins Hospital and at the Peter Bent Brigham Hospital came to Georgetown. He first worked with me in the Division of Endocrinology and Metabolic Diseases of the Department of Medicine, then assumed the directorship of the identical division in the Department of Pediatrics where he is now a Professor of Pediatrics. Dr. A. Martin, following her training in Pathology at Georgetown, has been collaborating with her husband Dr. M. Martin in his studies of the metabolism of hormones in obese children and adolescents.

To Doctor V. K. Vance who following his postdoctoral training at the Boston City Hospital, joined the Harvard faculty at the Peter Bent Brigham Hospital, then went to Buffalo as Director of Endocrinology and Metabolic Diseases at the newly formed State University of New York, Upstate Branch, and finally joined our faculty where he is a member of this division as well as a Professor of Medicine. His principal area of activity has been in the Fairfax Community Hospital where he is chief of its medical services. Dr. Lee spent the first few years, after his year of residency at the Georgetown University Hospital, in the Laboratory of Dr. G. Thorne at the Peter Bent Brigham Hospital in Boston; then in Worcester, Mass. at St. Vincents Hospital he isolated, and identified a vasodepressor material from renal medullary tissue as a specific Prostaglandin. He and his collaborators have continued this work next at the St. Louis U. School of Medicine, and now at the New York State U. School of Medicine Upstate Branch at Buffalo.

To Doctor James Pittman who has made many important contributions to our knowledge of thyroid physiology while at the University of Alabama. There he was Professor of Medicine and Director of the Nuclear Medicine Laboratory. He has been a member of our division for the past two years while working in the Veterans Administration's Central Office for scientific research in Washington. We are unfortunately about to lose Dr. Pittman because he is returning to the University of Alabama and will assume the deanship of that very important University School of Medicine.

The contributions of these members of the division will afford an insight into the variety of activities that occupy our interest. I hope that these succinct but significant papers will afford the readership of the Annals stimulating and useful information.

Each of these papers stresses the importance of correct and specific diagnosis as an essential facet of the therapy of human disease. That philosophy is of great importance in the training of all doctors and in the economical form of delivery of high quality medical care, that I am constrained to make the following strongly critical comments concerning the emergence of corporate entities, the so called "third parties" as solo practitioners of medicine.

I refer to the increasing frequency of *ex post facto* judgments by such corporations to the effect that medical care professionally recommended and supervised does not constitute a reimbursable expense to their premium paying policy holders, our patients. This corporate practice of medicine by such entities usually entails a contact between a physician and a patient, frequently after one or more previous diagnostic and therapeutic efforts. These have been directed at disease entities which seem reasonable on the basis of available data, but have either failed or have been only minimally effective in relieving a symptom complex. As emphasized in these papers, in addition to a very adequate historical and physical evaluation, some specific and at times highly sophisticated laboratory measurements are required. Some measurements are available but may frequently require, in the judgment of the physician, close control of the environmental variables for proper application and interpretation. The patient and occasionally the physician, always the hospital or laboratory, are informed by the patient's corporate practitioner that the recently completed evaluation was "diagnostic" not "therapeutic," and that at the worst no reimbursement will be made to the patient who has paid regular premiums, or at best only selected laboratory studies will be paid for by the corporate entity. These judgments are usually based on an audit of the patient's record carried out by a non physician employee of the corporate entity.

I understand that some physicians have begun to insist that their patients check with their corporate practitioners in medicine prior to the commencement of any evaluation, and that these corporate parties are responding with specific yeas and nays to such questions. For the trained and licensed professionals of medicine to permit such actions to go unchallenged is inexcusable. By permitting the unlicensed corporate entities to practice the delivery of health care in this fashion, we, the professional physicians, are demoting ourselves to the role of medical technologists. Thus, we become the vicarious employees of the insurance corporations permitting them to practice medicine with a major profit motivated economic bias.

At the moment these corporate entities are practicing largely after the fact. The information that these practitioners are utilizing in their judgment making process is usually gleaned from patient's records which are frequently incomplete at the time of the audit or evaluation. Obviously, their data base leaves much to be desired. The licensed physician usually responds to the corporate decision regarding medical care, aided and abetted by vehement protestations of the patient and occasionally by the hospital financial officer, by taking issue with the therapeutic decisions prescribed by or prohibited by the corporate entity. This is usually in the form of a rather detailed letter defending the professional's course of action with regard to the patient. The corporation in such an instance thus acts as both the practitioner in terms of its decisions regarding care (and as the judge and jury in the matter, since it is the active arbitor of the decision regarding the type of care it will afford the patient).

I have only deep pity for those licensed physicians who require that their patients obtain approval from their insurance carriers prior to any action by the doctor.

This is an insidious inversion of the physician's role and only physicians can correct this inappropriate behavior (practice without a license) on the part of such corporate entities.

I urge that all members of the profession begin to act in concert in some way to protect the welfare of all of our patients.

This usurpation of the role of the physician and the actions taken in the course of such role playing by the corporations often deny patients proper diagnosis and therapy. When examined by even the loosest cost benefit analytical techniques, this type of practice increases the cost of medical care tremendously not only to the patient involved, but to all participants in such corporate entities.

It is most distressing to recognize that in this region it is the so called "doctors" health insurance corporation, the Blue Cross-Blue Shield plan, which is the major perpetrator of this medical malapropism.

JOHN J. CANARY, M.D.
Professor of Medicine
Director of the Division of Endocrinology and Metabolic Disease
Georgetown University School of Medicine

Our Appreciation to

DR. JOHN J. CANARY

Professor of Medicine

Director of the Division of Endocrinology and Metabolic Disease

for coordinating this

Georgetown University Medical Center Issue.

Bobo's back at the big top

After a rheumatoid arthritic flare-up.

Butazolidin® alka   Geigy

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

rtant Note: This drug is not a simple analgesic. Do
dminister casually Carefully evaluate patients be-
starting treatment and keep them under close su-
sion. Obtain a detailed history, and complete
cal and laboratory examination (complete hemo-
, urinalysis, etc) before prescribing and at fre-
t intervals thereafter Carefully select patients,
ling those responsive to routine measures, contra-
ated patients or those who cannot be observed fre-
tly Warn patients not to exceed recommended
ge Short-term relief of severe symptoms with the
est possible dosage is the goal of therapy Dosage
ld be taken with meals or a full glass of milk. Sub-
e alka capsules for tablets if dyspeptic symptoms
r Patients should discontinue the drug and report
ediately any sign of. fever, sore throat, oral lesions
nptoms of blood dyscrasia); dyspepsia, epigastric
, symptoms of anemia, black or tarry stools or other
ence of intestinal ulceration or hemorrhage, skin re-
ons, significant weight gain or edema. A one-week
period is adequate. Discontinue in the absence of a
rable response. Restrict treatment periods to one
k in patients over sixty
ations Acute gouty arthritis, rheumatoid arthritis,
matoid spondylitis.
raindications: Children 14 years or less; senile pa-
s, history or symptoms of G.I. inflammation or ul-
tion including severe, recurrent or persistent dys-
ia, history or presence of drug allergy; blood
rasias. renal, hepatic or cardiac dysfunction, hy-
ension; thyroid disease; systemic edema;
atitis and salivary gland enlargement due to the
, polymyalgia rheumatica and temporal arteritis;
nts receiving other potent chemotherapeutic
ts, or long-term anticoagulant therapy
nings. Age, weight, dosage, duration of therapy, ex-
ce of concomitant diseases, and concurrent potent
otherapy affect incidence of toxic reactions. Care-
nstruct and observe the individual patient, espe-
the aging (forty years and over) who have
ased susceptibility to the toxicity of the drug Use
st effective dosage Weigh initially unpredictable
fits against potential risk of severe, even fatal, re-
ns The disease condition itself is unaltered by the
Use with caution in first trimester of pregnancy

and in nursing mothers Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid) Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage If edema occurs in patients over sixty, discontinue drug. *Precautions.* The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy The majority of these patients were over forty Remember that arthritic-type pains can be the presenting symptom of leukemia. *Adverse Reactions:* This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement (B)98-146-070-H(10/71)

For complete details, including dosage, please see full prescribing information

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

BU 9337

More than sleep

your choice of sleep medication is wisely based on more than sleep-inducing potential

sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dal (flurazepam HCl); no depression of cardiac or respiratory fur was noted in patients administered recommended or higher for as long as 90 consecutive nights.

In most instances when adverse reactions were reported, they were mild, infrequent and seldo quired discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. ness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

sleep for 7 to 8 hou without need to repeat dosage

No sleep r cation has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia pat given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer n time awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to re dosage during the night.

eep with nsistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration, with no need to increase dosage.

almane (flurazepam HCl) is a distinctive sleep medication—a
odiazepine specifically indicated for insomnia. It is not a bar-
te or methaqualone, nor is it related chemically to any other
ble hypnotic.

Vhen your evaluation of insomnia indicates the need for a sleep
cation, consider Dalmane—a single entity nonnarcotic, non-
urate agent proved effective and relatively safe for relief of
nnia.

DALMANE®

(flurazepam HCl)

When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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ROCHE LABORATORIES
Div., Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

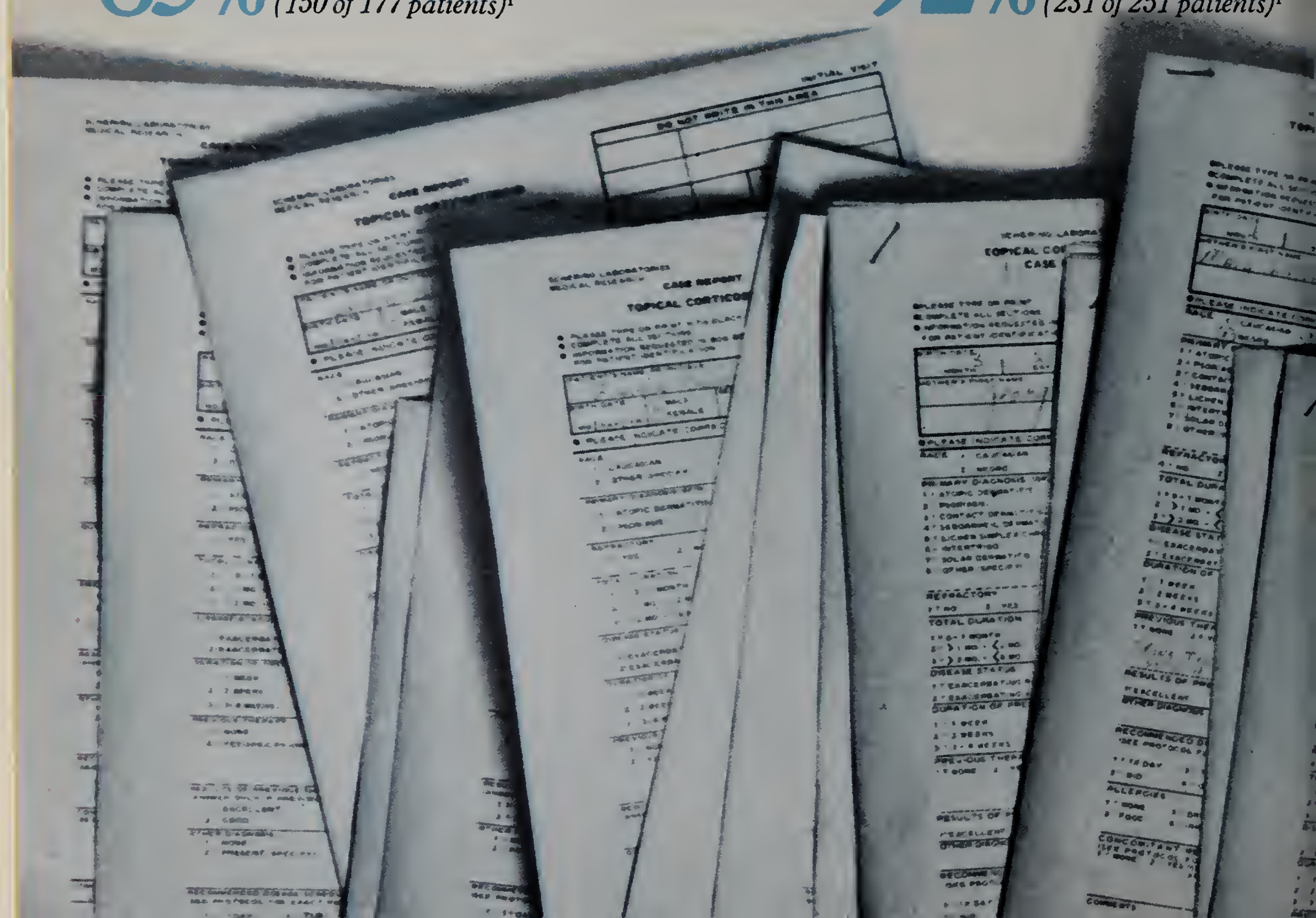
A topical steroid that has clinically succeeded

in study...after study...after study[1-6]

Excellent/good results

85% in psoriasis *(150 of 177 patients)*[1]

92% in atopic ecz *(231 of 251 patients)*[1]



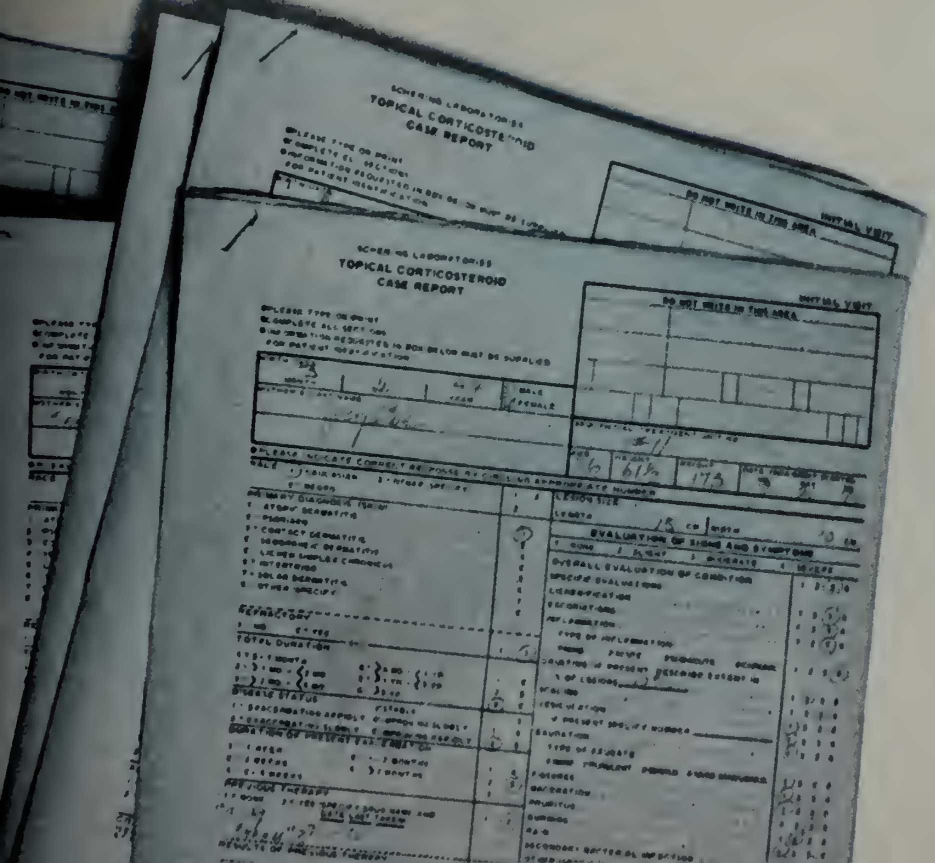
Valisone

brand of

betamethasone valerate (0.1%) Cream/Ointment

Plus economy *B.i.d. dosage often found effective!*
Available in 5, 15, and 45 Gm. tubes.

6% in contact dermatitis
(81 of 84 patients)[1]



SCHERING LABORATORIES
TOPICAL CORTICOSTEROID
CASE REPORT

DO NOT WRITE IN THIS AREA

INITIAL VISIT

Schering

CLINICAL CONSIDERATIONS:

Description VALISONE products contain betamethasone valerate (9-fluoro-11$_\beta$,17,21-trihydroxy-16$_\beta$-methylpregna-1,4-diene-3,20-dione 17-valerate). Each gram of VALISONE Cream 0.1% contains 1.2 mg. betamethasone valerate (equivalent to 1.0 mg. betamethasone) in a soft, white, hydrophilic cream of water, mineral oil, petrolatum, polyethylene glycol 10 monocetyl ether, cetostearyl alcohol, monobasic sodium phosphate, and phosphoric acid; 4-chloro-m-cresol is present as a preservative. Ea gram of VALISONE Ointment 0.1% contains 1.2 mg. betamethasone valerate (equivalent to 1.0 mg. betamethasone) in an ointment base of liquid and white petrolatum, and hydrogenated lanolin. VALISONE Cream and Ointment contain no parabens.

Indications VALISONE Cream and Ointment are indicated for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

Contraindications VALISONE Cream and Ointment are contraindicated in vaccinia and varicella. Topical steroids are contraindicated i those patients with a history of hypersensitivity to any of the components of the preparation.

Precautions If irritation develops with the use of VALISONE Cream or Ointment, treatment should be discontinued and appropriate therapy instituted. In the presence of an infection, the use of an appropriate antifungal or antibacterial agent should b instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled. If extensive areas are treate or if the occlusive technique is used, the possibility exists of increased systemic absorption the corticosteroid and suitable precautions shou be taken. Although topical steroids have not been reported to have an adverse effect on preg- nancy, the safety of their use in pregnant female has not been absolutely established. Therefore, they should not be used extensively in pregnant patients, in large amounts, or for prolonged periods of time. VALISONE Cream and Ointment are not for ophthalmic use.

Adverse Reactions The following local adverse reactions have been reported with topical corticosteroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, and hypopigmentation. T following may occur more frequently with occlusive dressings than without such therapy: maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Dosage and Administration Apply a thin film of VALISONE Cream or Ointment to the affected skin areas one to three times a day. Clinical studies of VALISONE have indicated that dosage only once or twice a day is often feasible and effective. AUGUST 1972

For more complete details, consult Scheri literature available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

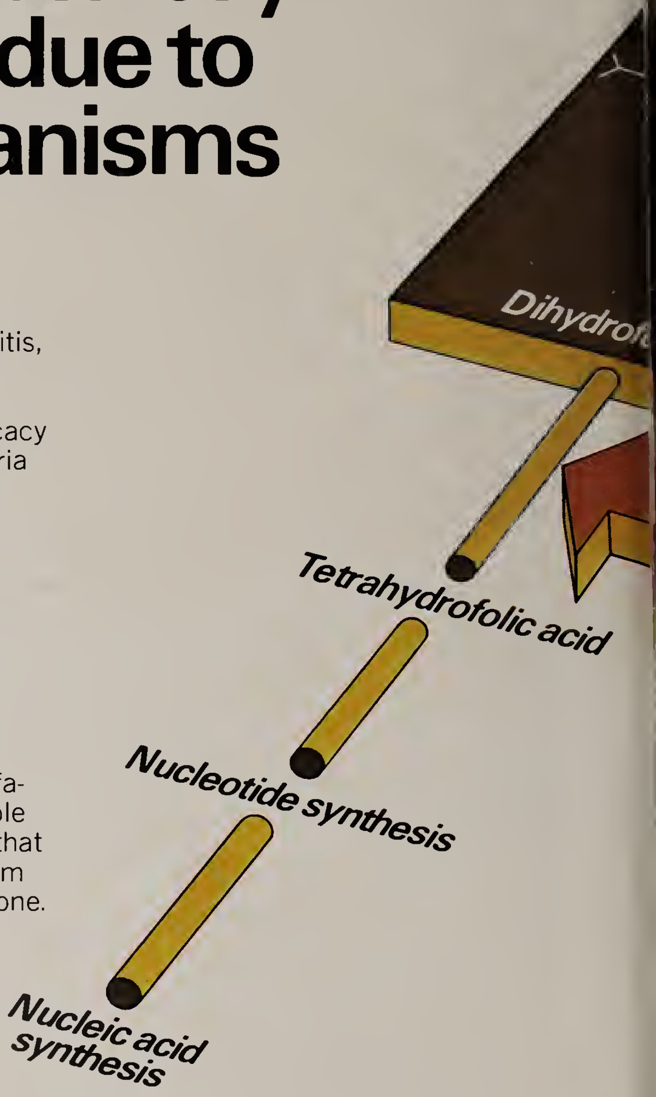
References: *(1) Files of Headquarters Medical Research Division, Schering Corporation. (2) Carter, V. H., and Noojin, R. O.: Curr. Therap. Res. 9:253, 1967. (3) Falk, M. S.: Cutis 2:788, 1966. (4) Goldblum, R. W.: Pennsylvania Med. 69:50, 1966. (5) Nierman, M. M.: J. Indiana M. A. 10:1184, 1966. (6) Zimmerman, E. H.: Arch. Dermat. 95:514, 1967.*

SLR-

ROCHE announces new BACTRIM™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

a new type of antibacterial for a two-pronged attack against chronic urinary tract infections due to susceptible organisms



Bactrim is highly effective in the treatment of these infections—primarily pyelonephritis, pyelitis and cystitis, when due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species). This efficacy is related to the unique mode of action against bacteria (see opposite page), an action that, in effect, makes Bactrim a new type of antibacterial.

Bactrim significantly superior to constituents in patients with obstructive complications

In the presence of obstructive uropathy, Bactrim has demonstrated efficacy which is superior to either sulfamethoxazole or trimethoprim alone against susceptible organisms. In addition, *in vitro** studies have shown that bacterial resistance develops more slowly with Bactrim than with either trimethoprim or sulfamethoxazole alone.

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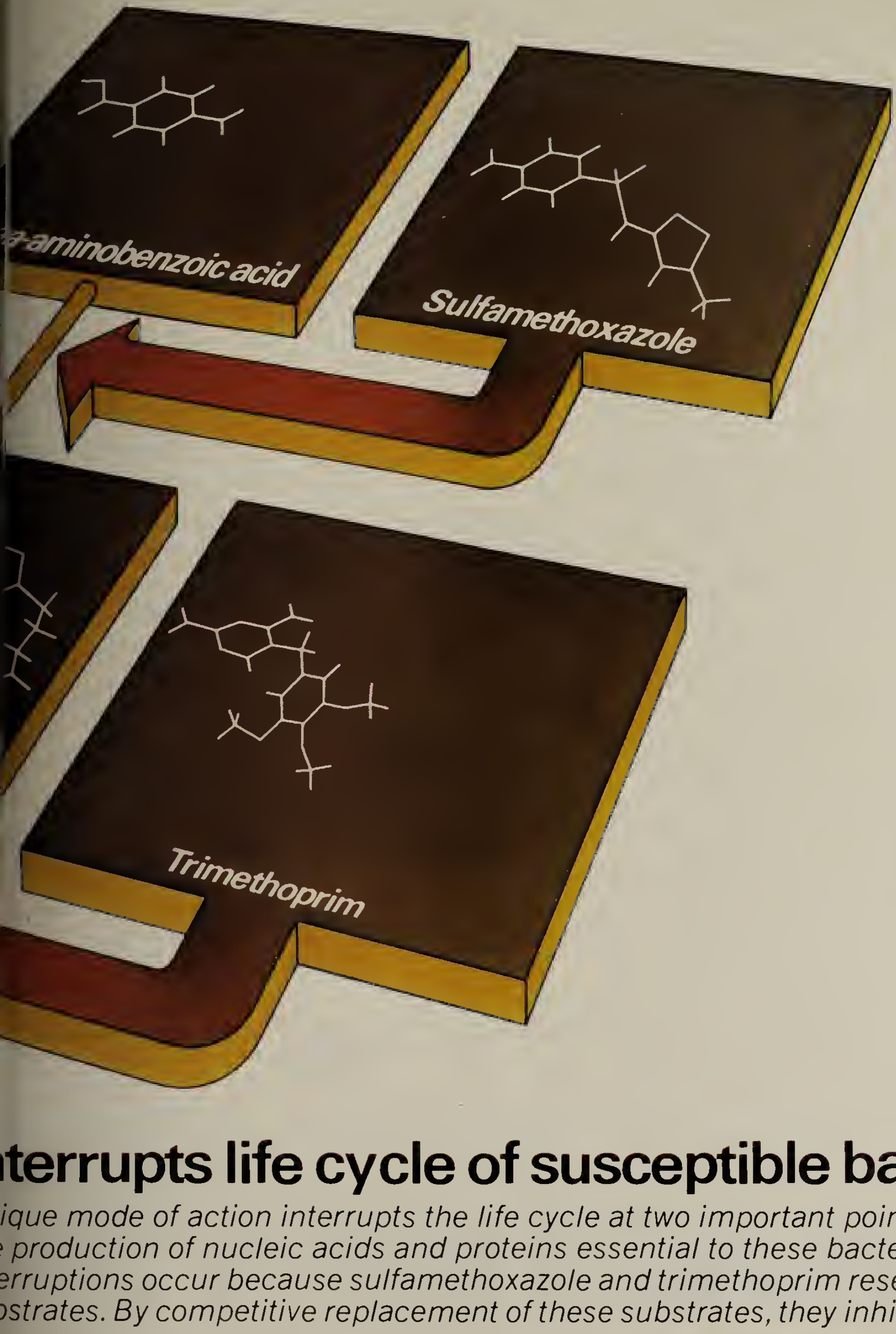
*Please note that clinical conclusions cannot be extrapolated from *in vitro* studies.



ROCHE

terrupts life cycle of susceptible bacteria

ique mode of action interrupts the life cycle at two important points, thereby impeding production of nucleic acids and proteins essential to these bacteria. These consecutive erruptions occur because sulfamethoxazole and trimethoprim resemble naturally existing strates. By competitive replacement of these substrates, they inhibit further synthesis.

new **BACTRIM**™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

Before prescribing, please see complete product information on last page of advertisement.

Excellent clinical response in chronic urinary tract infections

A multiclinic, double-blind study* of response to a ten-day course of therapy in 471† patients with chronic urinary tract infections demonstrated the superiority of Bactrim. On the 10th day after initiation of therapy, 91.7% (of 168 patients) showed significant bacteriological response to Bactrim compared with 81.2% (of 144 patients) to trimethoprim and 64.5% (of 155 patients) to sulfamethoxazole. In patients with obstructive complications, 10th day response was 94.8% (of 97 patients) to Bactrim, 72.9% (of 85 patients) to trimethoprim and 58.5% (of 94 patients) to sulfamethoxazole.

Excellent response maintained

Bactrim proved equally impressive in maintaining this bacteriological response. In the above study, after ten-day therapy with Bactrim, 68.4% of patients with chronic urinary tract infections maintained response for up to 42 consecutive days, compared with 59.7% with trimethoprim and 44.4% with sulfamethoxazole. In patients with obstruction, 70.8% of those on Bactrim maintained response for up to 42 consecutive days, compared
with 49.4% on trimethoprim and 38.8% on sul
methoxazole. The figures are particularly rema
able in cases with urinary obstruction—cases
regarded as being notoriously difficult to treat.

To date, low incidence of significant side effects

Although Bactrim demonstrated impressive cli
results, it is important to note that the incidenc
clinically significant adverse effects was low, m
nausea and/or vomiting, rash, leukopenia, SGO
increase and creatinine increase.

Bactrim should be given with caution to patien
with impaired renal or hepatic function, possib
folate deficiency and to those with severe aller
bronchial asthma. Adequate fluid intake must
maintained. Complete blood counts, urinalyses
careful microscopic examination, and renal fu
tion tests should be performed during therapy.

Currently, the increasing frequency of resistant
organisms is a limitation of the usefulness of
all antibacterial agents, especially in the treatm
of chronic and recurrent urinary tract infection

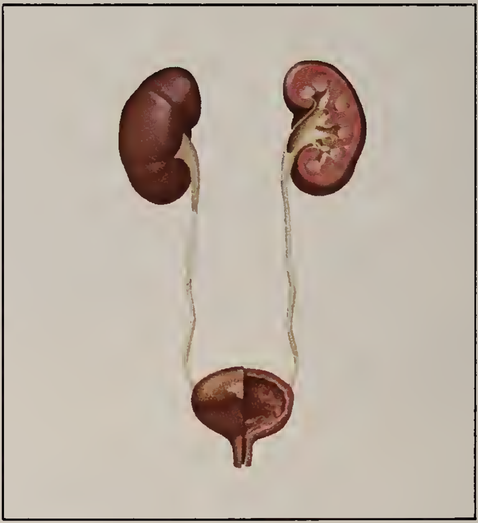
Usual adult dosage: two tablets every twelve h
for 10 to 14 days; no loading dose required.

---

* Data on file, Hoffmann-La Roche Inc., Nutley, N.J. 071

† 4 patients not available for evaluation at day 10.

Rx
Bactrim
Tablets #40
Sig: ii B.I.D.



new **BACTRIM**™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N.J. 07110

Before prescribing, please consult complete product information on facing page.

te Product Information:

tion: Bactrim is a synthetic antibacterial combination prod- ailable in scored light-green tablets, each containing 80 mg oprim and 400 mg sulfamethoxazole.

hoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. white to light-yellow, odorless, bitter compound with a molec- ight of 290.3.

ethoxazole is N^1-(5-methyl-3-isoxazolyl) sulfanilamide. It is ost white in color, odorless, tasteless compound with a mo- weight of 253.28.

Microbiology: Sulfamethoxazole inhibits bacterial synthesis /drofolic acid by competing with *para*-aminobenzoic acid. noprim blocks the production of tetrahydrofolic acid from di- olic acid by binding to and reversibly inhibiting the required e, dihydrofolate reductase. Thus, Bactrim blocks two con- e steps in the biosynthesis of nucleic acids and proteins ial to many bacteria.

studies have shown that bacterial resistance develops more with Bactrim than with trimethoprim or sulfamethoxazole

serial dilution tests have shown that the spectrum of anti- ial activity of Bactrim includes the common urinary tract ens with the exception of *Pseudomonas aeruginosa*. The fol- organisms are usually susceptible: *Escherichia coli, Kleb- Enterobacter, Proteus mirabilis* and indole-positive proteus s.

Representative Minimum Inhibitory Concentration Values for Bactrim-Susceptible Organisms
(MIC—mcg/ml)

ria	Trimeth-oprim alone	Sulfameth-oxazole alone	TMP/SMX (1:20) TMP	SMX
richia *l*	0.05—1.5	1.0 —245	0.05—0.5	0.95— 9.5
us spp. e positive	0.5 —5.0	7.35 —300	0.05—1.5	0.95—28.5
us *bilis*	0.5 —1.5	7.35 — 30	0.05—0.15	0.95— 2.85
iella- *obacter*	0.15—5.0	0.735—245	0.05—1.5	0.95—28.5

n Pharmacology: Bactrim is rapidly absorbed following oral istration. The blood levels of trimethoprim and sulfamethoxa- re similar to those achieved when each component is given Peak blood levels for the individual components occur one r hours after oral administration. The half-lives of sulfameth- e and trimethoprim, 10 and 16 hours respectively, are rela- the same regardless of whether these compounds are admin- as individual components or as Bactrim. Detectable nts of trimethoprim and sulfamethoxazole are present in the 24 hours after drug administration. Free sulfamethoxazole imethoprim blood levels are proportionately dose-dependent. eated administration, the steady-state ratio of trimethoprim amethoxazole levels in the blood is about 1:20.

nethoxazole exists in the blood as free, conjugated and pro- ound forms; trimethoprim is present as free, protein-bound etabolized forms. The free forms are considered to be the eutically active forms. Approximately 44 percent of trimeth- and 70 percent of sulfamethoxazole are protein-bound in the The presence of 10 mg percent sulfamethoxazole in plasma ases the protein binding of trimethoprim to an insignificant e; trimethoprim does not influence the protein binding of nethoxazole.

tion of Bactrim is chiefly by the kidneys through both glomer- iltration and tubular secretion. Urine concentrations of both nethoxazole and trimethoprim are considerably higher than e concentrations in the blood. When administered together Bactrim, neither sulfamethoxazole nor trimethoprim affects inary excretion pattern of the other.

tions: Chronic urinary tract infections (primarily pyelonephri- yelitis and cystitis) due to susceptible organisms (usually *li, Klebsiella-Enterobacter, Proteus mirabilis*, and, less fre- ly, indole-positive proteus species).

tant note: Currently, the increasing frequency of resistant organ- is a limitation of the usefulness of all antibacterial agents, espe- in the treatment of chronic and recurrent urinary tract infections.

aindications: Hypersensitivity to trimethoprim or sulfonamides. nancy and during the nursing period (see Reproduction es).

ngs: Deaths associated with the administration of sulfonamides been reported from hypersensitivity reactions, agranulocyto- plastic anemia and other blood dyscrasias. Experience with thoprim alone is much more limited, but it has been reported erfere with hematopoiesis in occasional patients. In elderly nts concurrently receiving certain diuretics, primarily thia- , an increased incidence of thrombopenia with purpura has reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Bactrim. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued.

At the present time, there is insufficient clinical information on the use of Bactrim in infants and children under 12 years of age to recommend its use.

Precautions: Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Adverse Reactions: For completeness, all major reactions to sulfonamides and to trimethoprim are included below, even though they may not have been reported with Bactrim.

Blood dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

Dosage and Administration: Not recommended for use in children under 12 years of age.

The usual adult dosage is two tablets every 12 hours for 10 to 14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

How Supplied: Tablets, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 1000; Prescription Paks of 40, available singly and in trays of 10. Imprint on tablets: ROCHE 50.

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Hypertension and Human Renal Prostaglandins

VERNON K. VANCE, M.D.* AND JAMES B. LEE, M.D.†

Introduction

The prostaglandins are cyclic fatty acids with a variety of biological activities on practically every organ system. Von Euler[1] has been credited with the discovery that extracts of semen or seminal vesicles caused uterine contraction and lowering of blood pressure. Furthermore, he characterized the active agents in the extracts as fatty acids and coined the term prostaglandins. Bergstrom[2,3] and co-workers isolated and identified two classes of prostaglandins, prostaglandin E(PGE) and prostaglandin F(PGF). A third class, prostaglandin A(PGA) was isolated, characterized, and identified by Lee and his associates[4-6] from rabbit renal medulla and was shown to have a potent blood pressure lowering effect, but no effects on nonvascular smooth muscle.

In addition to effects on uterine contraction and blood pressure, the prostaglandins have been found to be associated with hypothalamic, pituitary, thyroid, adrenal, and ovarian function as well as platelet aggregation, deformity of red blood cells, local and systemic inflammatory responses, immunological responses, intestinal secretion and motility, lipolysis in adipose tissue, contraction of the iris, and intraocular fluid pressure. Several reviews and symposia are available for perusal by the interested reader[7-10], and this paper will be limited to a discussion of the possible role of the renal prostaglandins and other lipids in the control of blood pressure.

TABLE 1. Prostaglandin A and E Concentration in Human Renal Tissue (picograms per milligram).

	Autopsy Specimens		Surgical Specimens	
	PGA	PGE	PGA	PGE
Cortex	37 ± 7*	49 ± 6	15 ± 3	29 ± 10
Outer Medulla	96 ± 30	110 ± 29	148 ± 46	220 ± 173
Papilla	336 ± 91	209 ± 52	1297 ± 247	1919 ± 444

* Standard Error of the Mean.

Renal Lipids with Vasodepressor Activity

The demonstration that homogenates of rabbit renal medulla produce sustained blood pressure depression in normotensive vagotomized rats[4,5] and subsequent identification of prostaglandins E2, F2α, and A2 from rabbit renal medulla[5,6] stimulated studies of vasodepressor substances in human renal medullas obtained from autopsy material. A crude acidic lipid extract (ALE) was shown to produce sustained (greater than 90 minutes) lowering of blood pressure in pentobarital-anesthetized, pentolineum-treated normal rats as well as a shorter stimulation of uterine contraction[11,12]. Partial purification of the crude lipid by silicic acid chromatography revealed that the active fraction was a fatty acid which did not have the same chromatographic characteristics as the prostaglandins. Furthermore, its duration of action was considerably longer than that of the prostaglandins.

Prostaglandin E and A concentrations in human kidneys obtained at autopsy or following surgical excision have been determined by a satisfactorily sensitive and specific radioimmunoassay[13,14]. These studies revealed the existence of concentration gradients for prostaglandins E and A in different zones of the kidney from papilla to outer medulla to cortex (Table 1). Concentrations of PGA did not differ significantly from those of PGE in cortex, outer medulla, or papilla, but both were higher in cortex, equal in outer medulla, and lower in papilla of kidneys obtained at autopsy as compared with those obtained surgically. The data suggest the probability that postmortem autolysis of prostaglandins occurs primarily in the papilla and the possibility that they may diffuse post mortem from papilla and/or outer medulla to cortex. PGA concentrations were found to be low in tissues from hypernephromas (renal cell carcinomas). Renomedullary bodies[15] (renomedullary interstitial cell tumors, fibromas of renal medulla[16]) were found to contain high concentrations of PGA, supporting the concept that the prostaglandins are synthesized by renal medullary interstitial cells.

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A third renomedullary lipid with antihypertensive activity has been extracted from renal medulla and medullary interstitial cells grown in tissue culture by Muirhead *et al*[17] and has been called "antihypertensive neutral renomedullary lipid (ANRL). The three antihypertensive lipids are compared in (Table 2).

TABLE 2. Renomedullary Antihypertensive Lipids

Substance	Extraction	Structure	Duration of Action
ALE (12, 13)	Acid	Fatty Acid	90 min.
ANRL (18)	Neutral	?	Days
PGA (5, 6)	Acid	Cyclic Fatty Acid	6–7 min.

ALE–Acidic Lipid Extract
ANLR–Antihypertensive Neutral Renomedullary Lipid
PGA–Prostaglandin A

Plasma Prostaglandins in Normal and Hypertensive Humans

The development of a radioimmunoassay for prostaglandins[13,14] has made possible the measurement of these substances in human plasma. Zusman,*et al*[18] have recently reported, in a study of seven normal persons, mean prostaglandin A levels of 1.6 ng/ml on an *ad lib* sodium diet. Levels decreased to a mean of 0.82 ng/ml (49%) after five days on a diet containing more than 200 meq sodium per day and increased to 2.14 ng/ml (34%) on a diet containing 10 meq sodium per day. These date are consistent with those of Lee, *et al*[19,20] who found that levels in normal subjects on *ad lib* diets were higher in those with low sodium excretion. In very recent studies by Zusman and his co-workers[21] and Lee, *et al*[20], both groups have shown that patients with essential hypertension have significantly lower plasma PGA levels than do normal subjects.

Table 3 demonstrates plasma PGA levels in blood obtained from the renal veins and vena cavae of six patients with essential hypertension and three with renal artery stenosis and hypertension. Levels in the veins from the involved (or more greatly involved) kidney were similar to those from patients with essential hypertension. Levels in the veins from the non-involved (or less involved) kidney were considerably higher.

Prostaglandin A Infusion in Hypertensive Patients

The infusion of PGA2 isolated from rabbit medullary tissue[22] to a hypertensive patient caused a fall in blood pressure and increases in heart rate and cardiac output. Infusion of PGA 1[23-26] in small amounts results in increased renal cortical blood flow associated with natriuresis, water diuresis, and (to a lesser extent) kaliuresis. Larger amounts cause a fall in blood pressure with a resultant decrease to normal of renal cortical blood flow, sodium and potassium excretion, and urine flow.

Discussion

The relationship between hypertension and the kidney is well known, but the mechanism by which the diseased kidney produces hypertension; or fails to protect the systemic circulation from developing it, is still not totally clear. The renin-angiotensin-aldosterone system has bee implicated, in the genesis of renovascular hypertension, but the etiolog of essential hypertension, where th earliest detectable abnormality is decreased renal cortical blood flow, c the hypertension associated with intrinsic renal disease has never satisfactorily been explained.

It has long been known that th presence of a normally functionin kidney protects experimental animal against systemic hypertension following renal arterial occlusion[27]. Furthermore, the hypertension which develops following bilateral removal o the kidneys (renoprival) can be reversed by successful transplantation o a normal kidney in animals o man[28,29].

The demonstration that blood pressure could be lowered by administration of renal extract[30] was followed by evidence that the active factor wa from the renal medulla[4,31].

Three separate and distinct vasodepressor lipids have been isolated and partially or totally characterized (see above and Table 2). Of these three only the prostaglandins have been studied in detail. Both prostaglandin A and E have antihypertensive properties, and administration o either via the renal artery results in increased renal cortical blood flow and natriuresis. It is possible that eithe PGA, PGE, or both normally are distributed intrarenally from medulla to cortex to regulate cortical blood flow. PGA may also be released into

TABLE 3. Plasma PGA Concentration in Inferior Vena Cava and Renal Vein (pg/ml)

Diagnosis	Inferior Vena Cava	Right Renal Vein	Left Renal Vein
Essential Hypertension (6)	1720 ± 137	1893 ± 95	1647 ± 125
Renal Artery Stenosis			
Left = Right	–	1614	1711
Left > Right	2753	2690	1523
Left Only	–	2156	1698

e systemic circulation, exert effects n the renal cortex, and directly ecrease systemic vascular tone. A ystemic effect of PGE appears unkely since it is metabolized to a iologically inactive form by one assage through the lung.

The recent demonstration, by two ifferent groups of investigators[20,21], f low circulating PGA levels in atients with essential hypertension upports the hypothesis that a defiiency of PGA may be an etiological actor in the pathogenesis of essential ypertension. The finding of decreased enal venous PGA levels in the veins of idneys with renal artery stenosis Table 3) suggests the possibility that ypertension develops because of a imitation in production of enough GA to overcome the pressor effects nedicated through the renin-angioensin-aldosterone system.

The saluretic and vasodepressor efects of PGA indicate a potentially mportant role for PGA or PGA nalogues in the treatment of human ssential hypertension. As Carr[25] has tated: "If PGA or a similar prostalandin can be formulated so it can be iven by mouth, it would be an ideal ntihypertensive agent".

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THE VIEW BOX

Prepared by
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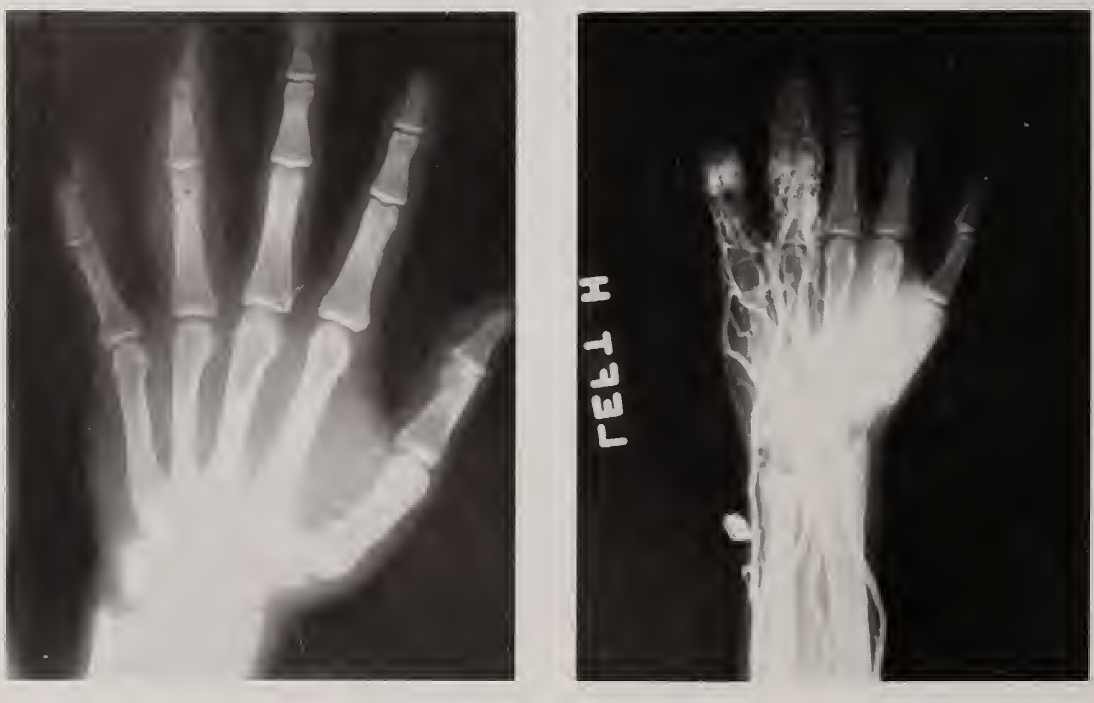
Twenty year old man with blotchy discolorations of skin found on routine physical examination.

(for diagnosis see page 434)



Obesity—A Form of Malnutrition

MALCOLM M. MARTIN, M.D., F.R.C.P.* AND ARLINE L. A. MARTIN, M.A., M.D.†

Introduction

Obesity is one of the major health problems in this country today. It is a serious disease with a heavy toll in morbidity and mortality. When body weight exceeds significantly the ideal weight for height, age and sex, hypertension, degenerative cardiovascular disease, diabetes mellitus, gout, lymphedema, venous stasis and respiratory problems are apt to develop. The concern of the physician, therefore, goes beyond the cosmetic distress which constitutes for most patients the primary motivation for seeking medical advice.

There is a consensus that obesity is a disorder of affluence with the major cause a caloric intake persistently in excess of caloric expenditure. The capacity of the body to store protein and carbohydrate is strictly limited and excess food in any form is converted into and stored as fat. Extensive literature deals with the "psychology of obesity" and the "obese personality" and ascribes obesity to emotional difficulties and gratification by overeating. The rare occurrence of obesity following encephalitis and frontal lobotomy are quoted in support of a psychogenic origin. Careful analysis of several studies, however, has indicated that the diagnostic spectrum of psychiatric disorders in unselected obese patients is in no way different from that in the general population. Obesity and its management, particularly in the teenager, may result in emotional disturbances; in most instances, however, the emotional problems and the obesity coexist but are in my opinion, unrelated. In some youngsters, psychological problems lead to overeating and obesity, in others to anorexia and weight loss. The notion that most, if not all, obesity is the result of pure gluttony, no longer obtains. Advances in methods for the assay of hormones in blood have had a great impact upon studies in obesity. Evidence has been found of many departures from normal in metabolic indices in obese subjects: these demand a fresh appraisal of the etiology of this most serious and disabling disorder.

With the recognition that the prognosis of obesity in adults is extremely poor and that a high proportion of obese adults were obese as children increasing attention has been paid to studies of this problem in childhood. With realization that the results of long term treatment of obesity in children are no better than the results in adults, emphasis has shifted to prevention to avoid a lifetime of dietary restriction. For rational means of prevention to succeed, a much clearer understanding is required of the etiology and pathogenesis of obesity in general, and the development, morphology and function of adipose tissue in particular.

Definition and Classification

Obesity may be defined as an excess of fat in the body, a condition readily recognized when the patient is obviously fat. When he is not that grossly obese some point of reference is required. Direct cadaver analyses have indicated an average fat content of about 12% in normal weight males and 20% in adult females[1]. Since this method of assessing the fat content is hardly applicable to clinical studies, indirect methods have been developed. Dilution techniques using isotopes (^3H_2O, ^{40}K, ^{42}K)[2] give estimates of body water and cell mass and can be used to calculate the amount of fat present. Densitometry[3], the measurement of body weight in and out of water, has also been applied. In actual practice, estimates of body fat obtained by reference to ideal body weight for height, age and sex, and skin fold thickness measured over the upper arm are most readily obtained. Since these correlate fairly well with results obtained by dilutional or densitometric methods they are the most widely used. In clinical studies obesity is usually said to be present when body weight exceeds ideal weight for height by more than 15 or 20%, or when triceps skin fold thickness exceeds 15 mm in males and 25 mm in females. While most investigators agree that obesity is a major nutritional problem, accurate figures as to prevalence are not available.

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Until recently obesity has been treated as though it were a single homogeneous disease entity. It is now thought that obesity is a truly multifactorial syndrome in which genetic and environmental factors, imbalance in food intake and energy expenditure, derangement in glucose and insulin metabolism, endocrine disorders and psychological processes may all contribute. Lesions of the ventro-medial hypothalamus, one of the most frequently studied experimental models in laboratory animals (immortalized by Dickens with the fat boy in "Pickwick Papers") are a rare cause of obesity in man. Inactivity is well recognized as a cause of corpulence and obese adolescents have been shown to be less active than their lean colleagues[4], but whether adolescent obesity is the cause or the result of inactivity has not yet been clearly defined.

Genetic factors, distinct from family habits, are difficult to assign in the human but do represent a varied group of defects in experimental animals in whom obesity may be inherited both as a dominant and a recessive trait[5]. Polygenic inbred and hybrid strains of mice are also known. This heterogeneity in the genetic expression of obesity in animals suggests that a similar degree of heterogeneity may exist in man.

At the present time any definition or classification of the obese state is purely arbitrary. Identification of the causative factor or factors, classification, prevalence and prognosis will have to await information on when and why the size of the adipose depot becomes abnormal. To what extent it will persist in adult life and predispose to pathological processes also remains to be elucidated.

Pathophysiology

Obesity is the result of an excess caloric intake over expenditure independent of whether the result of increased intake or decreased activity. Excess fat is stored in the body by increasing the size of existing fat cells, increasing the number of fat cells, or by a combination of the two[6].

A new method of studying subcutaneous fat by means of needle aspiration[7,8] has provided information concerning adipose tissue cellularity and metabolism. Fixation and separation of adipocytes from the tissue matrix has permitted individual cell counts by a Coulter counter. Measurement of lipid in the biopsy sample has made possible calculation of the average lipid content per cell. From the total body adipose mass, an estimate can be made of the total number of adipose cells in the subject. Cells of adults of normal weight contained an average of 0.6 μg of lipid and the average figure for total cell number was 26.8×10^9. Among obese subjects who had a childhood history of obesity not only was there 50% more lipid present per cell but the total cell number showed a three fold elevation. Weight reduction was accomplished by a decrease in adipose cell size, but not in number. In adults, adipose cell number appeared unaffected by dietary manipulation, and alteration in fat depots in adults was mediated solely by changes in cell lipid content. Hypercellular obesity thus seems to have the unfortunate consequence of inflicting the subject with a permanent increase in the mass of adipose cells.

Application of the same technique to studies in rats has shown that adipose tissue grows by an increase in both cell number and cell size[9]. By the 15th week of life, the cell number in the rat becomes fixed and further changes in the size of the adipose depot occur by an increase in cell size. Overfeeding or starvation beyond this age is ineffective in changing the final cell number. As in the human, once the adult cell number was attained it apparently could not be altered by dietary manipulation.

Data from earlier studies by McCance[10], however, indicate that rats subjected to nutritional deprivation very early in life do not achieve the same weight as non-manipulated litter mates despite adequate feeding later. Recent studies have confirmed these earlier observations and have shown that early nutritional influences can affect the number of the adult adipose cells in the epididymal fat pad of the rat. In addition, maternal protein calorie restriction during lactation has been associated with changes in adipose cell number in the young[11]. Early nutritional experience has thus been shown to cause a change in the size of the adipose depot by permanently affecting the number of adipose tissue cells. These observations and the fact that human obesity is accompanied by similar alteration in the number of adipose cells has led to the suggestion that early nutritional experience by virtue of its effect on cellularity may be of prime importance in the development of the obese state.

This hypothesis is in fact supported by recent studies. At all age levels obese children were found on the average to have not only larger adipose cells than non-obese children but more of them[12]. Cellular development occurred more rapidly in obese children, as early as two years of age. By age six, two subgroups could be distinguished within the obese population based on cell number: those with marked hypercellularity (exceeding normal adult values) and those with modest increases in cell number relative to non-obese subjects of the same age, but not exceeding normal adult values. The significance of these findings cannot be assessed at present but fit the clinical observation of two peaks for the onset of childhood obesity, one between birth and four or five years of age and another preceding the onset of puberty[13].

These findings also offer an explanation for the difference in response to dieting. The children who have already exceeded the normal adult range for cellularity may be expected to retain their obesity and respond poorly, whereas those within the normal range or below might do well. In teenagers who do poorly, studies of adipose tissue cellularity have indicated the presence of a hypercellular state which is unaffected by dietary manipulation (as in the adult) and which persists. It is clear, then, that early detection and prevention is imperative if lifelong obesity is to be avoided.

Control of Food Intake

In man, hunger and the desire to eat appear to be related to activity in the ventro-medial area of the hypothalamus which is thought to contain a "hunger center" and a "satiety center"[14]. The administration of glucose leads to a rapid amelioration of hunger. Glucagon, the hyperglycemic glycogenolytic hormone secreted by the alpha cells of the pancreas is even more effective in this respect. Based on studies with thioglucose, the ventro-medial area of the hypothalamus is thought to function as a "glucostat". A decrease in the arterio-venous glucose difference evokes the sensation of hunger whereas an increase produces satiety. Damage to the ventro-medial nucleus of the hypothalamus results in hyperphagia, decreased activity, and a rise in body weight[15]. This hypothalamic obesity is associated with an increase in the size of fat cells, but not hyperplasia.

Recent studies have provided new information concerning the neurochemical relationships that govern food intake. Food intake appears to be under adrenergic control which involves both alpha and beta-adrenergic receptors: alpha receptors mediate eating and beta receptors satiety[16]. Amphetamines have been shown to act as beta stimulators inhibiting food intake when injected into the lateral hypothalamus. Further studies of the adrenergic control of food intake may well provide a more rational approach to the management of the obese.

One of the factors that influences the hypothalamus in the regulation of feeding behavior is the frequency of food ingestion[17]. It has been found that eating one meal per day as opposed to three or more has metabolic consequences independent of the total caloric intake. Eating all one's food in one meal instead of spaced during the day increases blood cholesterol and impairs glucose tolerance and enhances lipogenesis. Epidemiologic studies have confirmed the negative correlation between the number of meals and obesity in school children: the fewer the meals, the greater the tendency towards obesity and increased skinfold thickness[18]. Thus, the frequency with which food is ingested is another controlling factor in subsequent metabolic events in the body.

Hormones and Obesity

Insulin is a potent lipogenic agent and chronic hyperinsulinism would favor the accumulation of body fat. Recent studies have confirmed hyperinsulinism as a feature of obesity both in the fasting state and after such varied stimuli as glucose, protein, glucagon, intravenous arginine and pharmacological agents such as tolbutamide[19-21]. This hyperinsulinism in the obese has been ascribed to as yet unresolved peripheral insulin resistance with compensatory overproduction of the hormone[22,23]. Whether these metabolic abnormalities precede or follow the development of obesity is still unsettled. To answer the question of whether hyperinsulinism is the cause or the result of obesity, a study was made of the metabolic effects of "iatrogenic" obesity in a group of human volunteers[24]. The subjects ingested two or three times their normal calorie diet and gained an average of 26% above their initial lean weight. It should be pointed out that some subjects reached their goal only with difficulty; others failed to gain even though consuming more calories than the successful volunteers. As the subjects became obese the metabolic and hormonal changes were as observed in other obese individuals. Plasma cholesterol and triglycerides became elevated as did plasma insulin; insulin sensitivity and carbohydrate tolerance decreased; there was progressive impairment in the growth hormone response to a falling blood sugar; fasting ketonemia decreased; steroid synthesis and excretion rose; and the respiratory quotient fell. Thus the increase in the adipose depot was associated with hyperinsulinism and insulin resistance.

In vivo and *in vitro* studies have provided some insight into the genesis of the hyperinsulinism in obesity. The demonstration *in vitro* of insulin resistence of hypertrophied adipocytes from obese subjects[25], and the *in vivo* insulin "resistance" in the intact obese human forearm[26] have identified adipose cell size as an important determinant of peripheral insulin sensitivity. However, it must be emphasized that only about 5% of basal and insulin stimulated glucose turn over involves adipose tissue[27]. Therefore, insulin insensitivity of muscle and liver must also be of importance. Hepatic gluconeogenesis is increased in obesity[28], presumably reflecting insulin insensitivity, since the enhancement of gluconeogenesis is occurring in the presence of elevated basal insulin levels that normally suppress this pathway[29]. Certain aminoacids, notably leucine, isoleucine, valine, phenylalanine and tyrosine have been found elevated in the obese[30] reflecting increased efflux of aminoacids from skeletal muscle presumably as a result of decreased insulin responsiveness of this tissue. The suggestion has been made in fact that this hyperaminoacidemia may constitute a stimulus for beta cell stimulation and the hyperinsulinemia of obesity[30]. The above studies simply confirm the existence of insulin resistance in the obese and suggest perhaps that peripheral insulin antagonism is primary in obesity.

Another study has suggested that the hyperinsulinemia of obesity may be related to dietary factors and that it may be an adaptation particularly to a high carbohydrate intake rather than exclusively the result of insulin resistance[31]. The insulin antagonism, in this context, then might be an adaptive mechanism to protect the obese person from hypoglycemic attacks the result of the excessive carbohydrate intake.

Whereas none of the studies provide an answer to the question of whether hyperinsulinism precedes the obesity or vice versa, they all attest to their interrelationship. The clinical experience of improved carbohydrate tolerance and diminished insulin response in the obese following weight reduction[25,32] suggests that the hyperinsulinism and associated abnormalities in the obese are secondary to, rather than the cause of, the adiposity.

Abnormalities in carbohydrate tolerance are a frequent concomitant of the obese state[19–23]. The abnormalities in glucose and insulin metabolism often are found in the absence of clinical manifestations of diabetes mellitus. Studies in adults have shown the obese diabetic to demonstrate both a delay in insulin release as well as a reduction in insulin reserve when compared to the obese nondiabetic, which led to the suggestion that all diabetes is essentially the result of insulin deficiency, absolute or relative[21].

Our own studies in children[33] have confirmed hyperinsulinism as a concomitant of obesity in that age group and have shown that the hyperinsulinemia and glucose intolerance relate to the duration of obesity rather than to the degree or age of onset of the adipose state. Of the 42 obese children studied, 28% demonstrated chemical diabetes with an excessive and delayed insulin response to glucose ingestion characteristic of maturity-onset diabetes. A further 26% had some impairment in carbohydrate tolerance with significant elevation in plasma insulin, and even the 45% with normal glucose tolerance showed some elevation in plasma insulin when compared to age matched controls of normal weight. With advancing age and duration of obesity, the obese children exhibited a spectrum of progressive glucose intolerance with increasing plasma insulin, with the children with chemical diabetes demonstrating the highest insulin responses contrary to the observations in adults. The findings suggest that obesity, hyperinsulinism and carbohydrate intolerance in childhood may be more than casually related and that maturity-onset diabetes may be maturity onset in terms of symptoms only and represent an entity clearly identifiable in childhood.

Growth hormone release by the anterior pituitary appears blunted in obese subjects, adults as well as children[20,27,33]. Thus, fasting levels of growth hormone are decreased as is the response to insulin induced hypoglycemia, arginine infusion, starvation and sleep. The late rise in growth hormone after oral glucose is also blunted. After weight reduction these changes revert to normal, at least in some subjects[34].

Growth hormone is known to stimulate cellular proliferation[35]. Studies in man and animals have demonstrated an effect of growth hormone on lypolysis only[36], but in growth hormone deficient children an increase in adipose cell number has been demonstrated some months after institution of replacement therapy[12]. At the present time the role of growth hormone in the development of obesity remains conjectural and further studies of its relationship to adipocyte proliferation are needed.

Adrenocortical function has been found increased in about half of the obese subjects studied, but the significance of this observation in relation to the development of the obese state is unclear[37]. Weight reduction is accompanied by a fall in steroid excretion but little is known of the effect of cortisol on human adipose tissue apart from the well known effect upon lipolysis.

Thyroid indices are normal in obese subjects and there is no evidence that thyroid malfunction plays any role in the pathogenesis of obesity[38].

To speculate concerning the etiology of obesity, deviations from normal in metabolic and hormonal profiles have been demonstrated in obese subjects. Their reversal to normal with weight reduction suggests that the metabolic and endocrine abnormalities are the result rather than the cause of the obesity. Hence one must turn to the neuro-endocrine control of the feeding pattern and early nutritional experiences for information regarding the development and ultimate size of the adipose mass in man.

A familial incidence of obesity has long been recognized and family studies have indicated that if one parent is obese, 50% of the children will become obese, and if both parents are obese 70 to 80% will do so[39]. Twin studies have indicated a significantly higher concordance rate in identical versus fraternal twins whether reared together or apart[40]. Furthermore the weight gain of natural children correlates well with that of their parents, a correlation lacking in adopted children[41]. Genetic influences unquestionably play a significant role in determining body weight, but so do environmental factors as suggested by the influence of early feeding on adipose cell number mentioned above.

As is usual with "nature versus nurture" the answer presumably is to be found in a combination of genetic predisposition and environmental influence. A newborn is probably endowed with a certain range of adipose tissue cellularity which becomes modified by external circumstances. It is tempting to suggest that over-feeding in infancy by providing calories in excess of requirements—possibly only in genetically predisposed infants—initiates increased lipogenesis and in turn increased insulin secretion which in time results in abnormal adipose tissue cellularity, excess accummulation of fat, decreased insulin sensitivity, a change in the "glucostat", further insulin hyperresponsiveness with further lipogenesis and ultimately obesity.

Whereas older children and adults are able to compensate for a high caloric diet resulting from the introduction of foods of high caloric density by reducing the volume of consumption, infants are able to do this only very imperfectly and the younger the baby the poorer the compensation. Artificial, "improved" high caloric density feeding, so widely advertised in our society, may in fact amount to an assault on the homeostatic control mechanism of the infant at a time when its regulatory function is not yet developed enough for it to defend itself. This would seem the more unfortunate in that the caloric thermostat once reset remains, it appears, irreversibly fixed.

The treatment of obesity is a perplexing and frustrating problem. Obese subjects are brought to the attention of the physician when the factors that promote the obese state are well established. All the physician has to offer is a variety of weight reduction programs unattractive to children and adults alike. In most cases young and old are obese and neither is prepared for a life of continuous dietary control and restriction. The result is a succession of attempts at weight reduction which end in a vicious cycle of weight loss and weight gain and the seeking out of one physician after another in search of a magic cure. Drugs are of little value in the long term management of obesity and should be avoided particularly in teenagers exposed to a drug oriented peer group.

In children overzealous dieting and severe dietary restriction is contraindicated. Weight reduction should be achieved by a decrease in body fat without loss of lean body mass. Sufficient calories and protein must be allowed to ensure normal growth and development. A 1000 calorie diet high in protein and low in carbohydrate and fat has proven successful in some cases provided adequate cooperation was forthcoming from parents and children. Full cooperation in the home and school are absolutely essential and without it all attempts at weight reduction are doomed to failure. As the children lose weight they become more active and thus enter into a reverse cycle of progressive weight loss with increasing activity. However, continuous attention to diet and weight are mandatory if relapse is to be avoided.

In adults who have been obese since childhood the prognosis is even poorer and conservative measures as outlined above have been largely futile. In severe refractory obesity, semistarvation, prolonged fasting and in selected cases surgical bypass procedures have been successful in bringing about a steady and significant weight loss[42]. However, these are radical and somewhat controversial measures which carry considerable risks. They should be reserved for massively obese patients who are severely handicapped or disabled by their adiposity and then only after failure of all conservative treatments. It must be emphasized furthermore that restoration of a more appropriate weight is but the first and perhaps easiest step in the treatment of obesity: maintaining the reduced weight is a much more difficult, vexing and frustrating problem and is unfortunately rarely successful.

In view of the gloomy prognosis of obesity it becomes most important that treatment be directed towards prevention rather than cure. Obesity frequently starts in childhood and even infancy, and obese children already demonstrate many of the predictive indicators of diabetes and degenerative cardiovascular disease. It is of the utmost importance that those caring for children realize the ultimate seriousness of obesity and institute the proper measures early in life as excessive weight gain first manifests.

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Some Thoughts on the Medical Management of Renal Stones*

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Urinary lithiasis, an enigma, continues to cause worldwide morbidity and mortality. The malady is of great historical interest, with good descriptions of the entity in the earliest scientific literatures: in Sumerian cuneiform, in Talmudic and Persian scripts, and in the early Vedic hymns of India in Sanskrit. The period covered by these sources extends from the 5th to the first millenium B.C.[1].

Hippocrates (460–370 B.C.) described both upper and lower urinary tract stone and the syndrome of renal colic. He recommended a large fluid intake as a means of therapy. Despite his well-recognized surgical skill, he stated in a part of his famous oath "I will not cut persons laboring under the stone but will leave this to be done by men who are practitioners of this work." This admonition effectively hindered concerted attack upon the cause of urinary stones for many hundreds of years, separating those who treated the common lower tract stone surgically from all others. This historic spectrum has been well reviewed by Butt[1].

TABLE 1. Stone Districts

Southeastern United States
Netherlands
Czechoslovakia
Bulgaria
Volga River Valley
Turkistan
Northeast & East Africa
Madagascar
Israel
Turkey
Spain
Eastern France
Southeastern France
Northern China
Western England
Southeastern England
Iran
Iraq
Afghanistan
Northwest India
East India
East Indies
Thailand
South China
Japan
Iceland
Greece
Northern Chile
Central Chile
Southeastern Argentina
Northeastern Brazil
Southern Brazil

The preponderant type or location of calculi common to each region is not shown. See text.

Geographic features must be emphasized. Before the Industrial Revolution, the majority of stones were bladder or lower urinary tract, composed chiefly of mixed urates. Since the late 19th and early 20th century, the period of the Industrial Revolution, in the more prosperous and technologically advanced societies (particularly those of Western Europe), urban areas in the less developed countries, and in North America and Australia, the anatomic site of stone occurrence has shifted from the lower to the upper urinary tract. Concomitantly, the crystal contents of the stones have changed from urate to calcium salts, largely of the oxalate type. In Table 1, are shown the stone districts of the world with a higher than usual incidence of stone. In this table no attempt is made to differentiate the principle occurrence of lower or upper urinary tract stones in these geographic regions. It is obvious that local climatic factors, physical work load, fluid intake, and diet are of importance in the genesis of stone in many of these areas.

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Regional economic factors must also be stressed[2,3,4,5]. These differences and their relation to urinary stone formation are emphasized in Table 2. In the United States, the southeastern portion of the country is the principle stone region or district. The most significant contribution to the definition of this area was made by Boyce and associates in 1954[6]. Several excellent reviews of many aspects of the problem of urinary tract lithiasis have appeared[7,8,9,10].

TABLE 2. Stone and Economy

Economy	Agrarian	Mixed	Technical
Technology	Under Dev.	Some	Developed
Age	Child	Mixed	Adult
Sex	Male	M > F	M = F
Site	Lower	Mixed	Upper
Type	Urate	Mixed	Ca Salts
Diet Staple	Grain	G > Prot.	Prot.
Protein. PO_4	Low	Moderate	High

The physical chemistry of the urine is etiologically important in stone formation. To be effective, therapy must result in some alteration in the chemical composition of that biologic fluid. The changes in urine which favor stone formation may be considered under two major headings: (A)—those changes which increase the urinary concentration of crystalloids, i.e. a reduction in the urine volume or an increased excretion of calcium, oxalate, cystine, uric acid, xanthine, hypoxanthine, and ammonia; and (B)—those chemical changes favoring crystallization at normal concentrations of some of the above substances. These latter changes may be brought about by alterations in pH, increased content of protein materials capable of forming stone matrix, stasis, the presence of foreign bodies or of the normally protective substances such as magnesium ions, citrate and other complexing substances, pyrophosphates, and other as yet unidentified substances.

The physician cannot consider the diagnosis and treatment of urinary lithiasis as a simple problem. A large number of clinical circumstances can produce alterations in one or both of these major chemical characteristics of urine favoring stone formation.

Table 3 affords an overview of the majority of etiologic factors which must be considered in the evaluation of a patient with urinary lithiasis. In the regions of the world where bladder stones are common, occupations (particularly those which can lead to dehydration) appear to be of some importance. Long periods of arduous physical work in hot, dry climates without substantial increase in water

TABLE 3. Etiologic Factors

General	Anatomic	Deficiencies Medications Extrinsic Factors	Systemic Disorders	Tubular Dysfunction Glomerular Dysfunction
Geography	Anomalies	$Al(OH)_3$ Gels.	Immobilization	Proteinuria
Climate	Obstruction	Alkalizing Agents	Osteoporosis-acute	R.T.A. (distal)
Race	Infection	Analgesics	Thyrotoxicosis	Aciduria
Age	Bleeding	Corticoids	Vit. D Intox.	Sarcoidosis
Sex		Glycols	Hyperparathyroidism	PTH Lack
Diet		Carbonic Anhydrase (INHB)	Sarcoidosis	Calciuria
Occupation		Silicates	Neoplasia	Glycinuria
		Uricosurics	Oxalosis	Oxaluria?
		Furosemide	Acidosis	
		Foreign Bodies	Beryllium Poisoning	
		Magnesium	Sodium Loading	
		Molybdenum	Xanthinuria (molyb)	
		Pyridoxine	Gout	
			Parasites	
			Cushings	
			Cystinuria	
			Hypoparathyroidism	
			Genetic	
			Growth Hormone Excess	
			Water Diuresis	
			Glucosuria	

intake predisposes to highly concentrated urine and much more frequent formation of stones[11]. In those regions where upper urinary tract stones are more frequent, the incidence of such stones is greater in those sedentary workers who do not ingest sufficient fluids. The high incidence in members of airline flight crews who spend substantial periods of time seated in carefully regulated environments has been noted[9]. The types of tubular dysfunction of etiologic importance are those which lead to increased concentrations of crystalloids in the urine or alterations of urine pH. The question mark following oxaluria is to indicate that in the past, reports of a specific renal tubular oxalate reabsorptive defect have appeared. However, hyperoxaluric patients without causes of secondary oxaluria are now considered to represent examples of either of two inborn systemic metabolic defects[12]. The recurrent formation of oxalate stones by patients with small intestinal disease is caused by the large quantities of glycine bile salts which are transported to the large intestine, absorbed and then converted by the liver into oxalate, leading to hyperoxaluria and stone formation[13].

The etiologically most frequent systemic disorders leading to stone formation are those which produce hypercalciuria. Much less frequent are those in which stones are the result of altered excretion of other specific substances such as cystine, xanthine, or uric acid. Xanthuria in sheep has been related, in one study, to a molybdenum deficiency, and this rare cause of stone requires further study[9].

An infrequently cited observation, but in my opinion an important one, is the relationship between medications, specific deficiencies and urinary lithiasis. Tubular damage produced by analgesic agents is well recognized and can lead, many years after their discontinuation, to the formation of stones[14]. The marked calciuria and phosphorus depletion resulting from aluminum hydroxide gel therapy can produce stone formation in certain individuals. Other medications (such as furosemide, which produces hypercalciuria in individuals who are well supplied with sodium and carbonic anhydrase inhibiting agents each capable of producing an alkaline urine) can lead to stone formation. Pyridoxine has been linked to oxalate metabolism and may, in patients with severe deficiencies of this vitamin, lead to an increase in urinary oxalate excretion and consequent stone formation.

An essential part of the treatment of urinary lithiasis is the evaluation of the patient. The majority of external, systemic or local mechanisms capable of producing urinary lithiasis can be defined and correctly managed by obtaining a detailed history, performing a complete physical examination, and obtaining a sufficient number of accurate laboratory studies. If the presence of any of the many specific causes can be defined it can usually be effectively managed. The physician confronted with patients with urinary lithiasis, in whom the possible etiologic mechanisms for which specific therapy exists have been excluded, must still attempt to alleviate the symptoms and at least modify the probably causes.

The substances which are generally recognized as being of value in the medical treatment of renal stones, with their beneficial and detrimental actions, are listed in Table 4.

A high water intake is useful since it leads to a reduction in the concentration of stone related ions in the urine. However, when excesses are ingested by patients whose urines contain large amounts of complexing agents which bind such active ions, the opposite effect may result by increasing the dissociation of these ions and favoring crystallization.

A high orthophosphate intake is

TABLE 4. Actions of Therapeutic Agents

	Urinary Effect	
Agent	Beneficial	Detrimental
H_2O	Lowers ion concentration	Raises ion concentration by diluting complexes
PO_4 load	Raises pyrophosphate Lowers calcium content	Elevates phosphate
Taurine	Increases T/G bile salts Decreases glycine formation (colon), decreases oxalate excretion.	None
Magnesium	Substrates for Ca, in crystal lattices inhibits crystal epitaxy. Complexes c̄ oxlate?	Complexes c̄ citrate. Crystal formation in alk. urine c̄ NH_4, Na and PO_4
Alkali	Elevation urine pH, lower urinary Ca & PO_4. Elevates citrate	Elevation Urinary pH
Low Oxalate	Lowers Oxalate	Elevates Ca
Thiazides	Lowers Calcium, elevates pyrophosphate	Raises pH
Xanthine Oxidase Inhibitors	Decrease uric acid production and excretion	Increase xanthine and hypoxanthine excretion
Penicillamine	Solubilize cystine in urine	Hematologic reactions Other allergic reactions

frequently useful in the treatment of calcium containing urinary stones. I have found that it is most useful in the form of salts of orthophosphoric acid, particularly the potassium acid phosphate salt. Inorganic phosphorus produces its beneficial results both by reducing urine calcium ion concentration and by increasing pyrophosphate concentration in the urine; both effects reduce the formation and growth of calcium containing crystals[15,16]. The resulting increased concentration of orthophosphate in the urine, however, under certain circumstances may outweigh these benefits, as in a urine in which an active infection is in progress[17].

Magnesium, usually administered in the form of capsules of magnesium oxide, is also useful in treating calcium containing urinary stones[18]. A possible mechanism recently proposed by Lonsdale[17] for its beneficial effect depends upon the fact that magnesium ions can substitute for calcium ions in calcium crystals. Because the radius of the hydrated magnesium ion is smaller than that of the calcium ion, substitution of a magnesium ion for a calcium ion in such a growing crystal can alter the geometry of the crystal lattice and reduce further crystal growth. This effect presumes that such crystal growth occurs by the phenomenon of epitaxy[17]. Magnesium would not be indicated, in my opinion, for the treatment of stone formation in patients who have an active infection present in the urine. The presence of an elevated urinary pH would also be an important further prohibition since under such circumstances the formation of magnesium ammonium phosphate or struvite stones would be facilitated[17].

The administration of taurine in doses of three grams three times daily by mouth has been shown to be very beneficial for those patients who form oxalate stones with the hyperoxaluria of small intestinal dysfunction. The mechanism, which has been quite well demonstrated, is to increase the taurine to glycine bile salt ratio, decreasing glycine absorption from the colon and thereby reducing oxalate formation by the liver and its subsequent urinary excretion[13]. No specific detrimental effects from taurine feeding in that circumstance have been reported. In individuals with other mechanisms for oxaluria, reductions in urinary oxalate excretion may be accomplished by administering diets low in oxalate content, by the addition of therapeutic amounts of pyridoxine, and by insuring the excretion of dilute urine. However, at present, medical therapy for such individuals leaves much to be desired.

The use of alkali generally, in the form of sodium bicarbonate in sufficient dose to elevate urine pH, is of definite value in patients with urate and cystine stones. This increases the solubility of these ions in urine and in conjunction with an adequate water intake can be very useful. Alkali therapy also reduces urinary calcium and phosphate excretion and elevates citric acid excretion. The latter is an effective calcium ion complexing agent reducing calcium ion concentration.

Xanthine oxidase inhibition is useful in the management of recurrent uric acid stone formation, particularly in the patient with hyperuricemia. This medication is a very useful adjunct in patients who form uric acid stones with normal levels of serum uric acid. Such individuals usually are those who have an acquired inability to produce an alkaline urine: they characteristically excrete an excessively acid urine in which uric acid stones may form even when the concentration of urinary uric acid is normal[19]. Alkali sufficient to elevate urine pH, plus water, is the most effective therapy for such stone forming patients. However, concomitant reduction in the formation of uric acid and hence its filtered load can be beneficial. Despite the fact that increased serum concentrations of xanthine and hypoxanthine result from the action of the xanthine oxidase inhibitor and the corresponding increase in the urinary excretion of these substances might be hazardous, it has not yet led to a significant reported increase in such stones although frequently used[20].

Table 5 schematically demonstrates the therapeutic approach that I have used for the medical management of renal lithiasis. In general, all patients are benefited by a more dilute urine produced by an increased water intake. Orthophosphate, usually in the form of its potassium acid salt to produce an intake of between 1.5 and 2.0 grams of inorganic phosphorus per day in excess of diet, has proven to be very useful in the vast majority of recurrent calcium stone forming patients whether their stones are of the idiopathic type or are associated with idiopathic hypercalciuria. The heavy form of magnesium oxide in 500 mg capsules, one capsule two or three times daily with meals, has also been useful in the idiopathic stone forming group as well as in some patients with the hypercalciuria of hypoparathyroidism. In such patients, phosphate is contraindicated and the benzothiadiazine drugs are generally ineffective. In the case of both magnesium and phosphate salts, the principal side effect has been the induction of looseness of stool or actual diarrhea. This has usually correlated well with dosage and is best managed by reducing the dosage to the level of intestinal tolerance.

The benzothiadiazine diuretic group, principally represented by thiazide and hydrochlorothiazide, if tolerated has proven to be effective in the management of certain patients with stones[21]. This is particularly true of those with idiopathic hypercalciuria. This group of compounds is useful as diagnostic as well as therapeutic tools. If the patient who fulfills the criteria for idiopathic hypercalciuria (*i.e.*, a normocalcemic patient with hypercalciuria on a reduced cal-

TABLE 5. Medical Rx Stones

(1)	(2)	(3)	(4)	(5)	(6)
H_2O	PO_4	Mg	Benzoth.	HCO_3 C-A inh.	Xanth. Ox. inh.
All	Hypercalcur. Blad. Idiop.	As in 2 Hypopara	As in 2	Urate cyst.	Urate

The several useful therapies are numbered 1–6, and the following abbreviations used. Under item 2, Blad. refers to bladder stone, Idiop. refers to idiopathic stone. Under item 4, Benzoth. refers to Benzothiadiazine diuretics. Under item 5, C-A inh. refers to Carbonic Anhydrase Inhibitors and cyst. refers to cystine stones. Under item 6, Xanth Ox. inh. refers to Xanthine oxidase inhibitor.

cium intake) responds to the thiazide diuretic with a sustained hypercalcemia as well as a 35-65% reduction in urine calcium excretion, this response favors the presence of a parathyroid hyperfunctional state. It warrants exploration for primary hyperparathyroidism. In our experience, patients without hypoparathyroidism respond with a 35-65% reduction in urine calcium excretion and, in the absence of parathyroid hyperfunctional abnormalities, fail to develop sustained hypercalcemia. For patients who are producing calcium stones, and who respond in such a fashion and tolerate the diuretic material (*i.e.*, do not become severely hyperuricemic or develop allergic reactions or unpleasant gastrointestinal symptoms) such diuretic materials can be used therapeutically in doses ranging from 50-100 mg as hydrochlorothiazide per day for prolonged periods of time. If potassium supplements are needed, these can easily be supplied in the form of fruit juices or some of the carbonated beverages which are high in potassium; in the patient who has a problem with body weight, potassium can be supplied by any of the available medicinal preparations. I have thus far followed approximately ten such patients for periods of up to five years with a remarkable reduction in the frequency of stone formation and freedom from other problems. However, in a number of other patients quite dramatic hyperuricemia developed, and others have had allergic skin reactions which prohibited the use of these medications.

For treatment of those individuals with urate or cystine stones, the use of bicarbonate as a means of alkalization, and water, constitutes the most important aspect of therapy. It is possible to take advantage of the carbonic anhydrase diuretics by administering doses of 500 to 1000 mg at the hour of sleep. This insures a relatively alkaline urine over the night and avoids the necessity of the patient's arising in the early hours of the morning to ingest more alkali. For the hyperuricemic uricosuric individual with stones, or for the uric acid stone forming individual without hyperuricemia, the administration of xanthine oxidase inhibitors is also to be recommended.

For the treatment of cystine stones, a diet low in protein and a very high water intake are useful. The addition of alkali as in the uric acid stone forming group is also useful, but the high sodium load can produce unwanted effects on the blood pressure. Penicillamine, which acts to increase the solubility of the dipeptide cystine, can be helpful though the high incidence of toxic reactions limits its use to those few patients with cystine stones who fail to respond to the simpler measures[22].

For patients with small bowel disease who form recurrent oxalate stones, I would recommend the use of the amino acid taurine as discussed earlier. For those individuals with the rare metabolic errors of oxalate metabolism, diets low in oxalate content, with pyridoxine, may be beneficial in conjunction with an increased fluid intake to produce a dilute urine.

This medical approach to the management of patients with renal stones, coupled with competent urologic evaluation and treatment where indicated, affords the physician an opportunity to approach the patient with renal stones with a definite plan of action. Modifications of or combinations of therapy are frequently indicated and can be applied with expectations of many favorable responses.

A very recent study indicates that enhancement of absorption of dietary oxalate underlies the hyperoxaluria of patients with ileal vesection and that diets containing less than 4.0 mg. of oxalate per day abolish the hyperoxaluria[23].

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THE VIEW BOX

(from page 422)

DIAGNOSIS: Angiomatous malformation 4th and 5th digits of the left hand.

The plain film shows soft tissue swelling of these digits with prominent vascular impressions on the proximal phalanges of the 4th and 5th digits and middle phalanx of the 5th digit.

The Arteriogram shows multiple tortuous and dilated vascular channels with multiple feeding arteries and draining veins. Most angiomatous malformations of the upper extremity involve the peripheral vessels of the hand, although they may occasionally be more proximal. Most cases tend to recur following proximal ligation because of rapidly developing collateral circulation.

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Varieties of Hypothyroidism

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The great majority of patients with hypothyroidism have their disease as the result of a lesion of the thyroid gland itself. Watanakunakorn *et al* found that about 96% of all hypothyroid patients were suffering from lesions of the thyroid gland per se[1]. The purpose of this brief review is to emphasize that the hypothyroid state can result from lesions in at least two, and perhaps three, other sites in the body as well. Although such instances constitute less than one-in-twenty of hypothyroid patients, failure to recognize such a state can result in inappropriate treatment and a catastrophic outcome.

Classification of Hypothyroidism

A classification of hypothyroidism according to site of the lesion and, to the extent possible, pathogenesis is given in Table 1. As has been previously pointed out[2], the only major gross point regarding the pathogenesis of hypothyroidism missed by the Myxedema Committee of the Clinical Society of London in their classical study[3] was that the disorder could be caused by lesions in thypituitary (and higher sites) as well as loss of the thyroid gland itself. This is not surprising, however, considering that neither pituitary function nor parathyroid function was understood at that time. (Convulsions resulting from surgical extirpation of "the thyroid" probably resulted in some cases from concomitant removal of the parathyroid glands, particularly in animal studies[3].) However, the Committee systematically related myxedema to loss of the thyroid gland for the first time and gave this explanation of the pathogenesis of the disease sufficient prominence and documentation to assure lasting acceptance of the concept[3,4].

TABLE 1. Varieties of Hypothyroidism, By Site of Lesion and Pathogenesis

- I. THYROIDAL (PRIMARY) HYPOTHYROIDISM
  - A. Loss of thyroidal mass
    - 1. Hashimoto's thyroiditis ("spontaneous" myxedema)
    - 2. Overtreatment of thyroid disease
      - a. Surgical
      - b. Radioiodine
  - B. Cryptothyroidism
    - 1. Lingual thyroid with hypothyroidism
    - 2. Sporadic athyreotic cretinism
  - C. Metabolic blockade
    - 1. Drug induced (e.g., methimazole, propylthiouracil, thiocyanate)
    - 2. Gene induced
      - a. Iodide "trap" defect
      - b. Peroxidase defect
      - c. Coupling defect
      - d. Deiodinase defect
      - e. Circulating iodoalbumin syndrome ("NBEI syndrome")
      - f. Thyroidal resistance to pituitary TSH
- II. PITUITARY (SECONDARY) HYPOTHYROIDISM
  - A. Postpartum infarction (Sheehan's syndrome)
  - B. Tumors (especially chromophobe adenoma)
  - C. Granulomas and other destructive lesions
- III. HYPOTHALAMIC (TERTIARY) HYPOTHYROIDISM
  - A. Temporary
  - B. Permanent
- IV. PERIPHERAL HYPOTHYROIDISM

In 1914 Simmonds described patients with marked asthenia leading to death. They also showed absence of the pituitary at autopsy[5,6]. Shortly thereafter P. E. Smith demonstrated that hypophysectomy in the rat is followed by atrophy of the thyroid as well as other glands[7]. Finally, in the late 1920s and early 1930s pituitary thyrotropin (TSH, thyroid-stimulating hormone) was identified[8], thus setting the stage for discovery of pituitary hypothyroidism.

In 1938 Hertz and Castleman had a patient with an illness diagnosed as hypothyroidism and treated with desiccated thyroid alone[9]. Instead of showing the characteristic improvement expected in such a situation, the patient worsened and died. Autopsy showed that the thyroid, though somewhat atrophic, was clearly present, but the pituitary was absent[9].

Shortly after this experience, Lerman had a patient who displayed a

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similar poor response to treatment with thyroid alone. She then failed to show up for a clinic appointment, and Dr. Lerman drove to the patient's house, found her semi-stuporous, and personally carried her to his car and brought her back to the Massachusetts General Hospital[10]. There she rapidly improved with administration of adrenal cortical extract and, interestingly, salt. This patient then was maintained on similar therapy until death, after which the case report was published[11]. These experiences received wide publicity among the teachers of American medicine , and the danger of adrenal insufficiency occuring in a hypopituitary patient treated with thyroid alone was stamped in the mental notes of physicians caring for hypothyroid patients.

In fact, this danger, though real and avoidable, may have been over-emphasized. Peters *et al* later showed that when the dose of thyroid is gradually raised, these patients may tolerate the medication without precipitation of adrenal crisis[12]. However, in my experience with several such patients, they never feel well, are brittle, and give one the impression of being on the brink of catastrophe. There is no reason with modern diagnostic methods not to treat them with all three replacement drugs (thyroid, glucocorticoids, and gonadal steroids) whenever there is any doubt as to the nature or site of the lesion.

Because of the negative thyroid-pituitary feedback loop, the laboratory hallmark of "primary" thyroidal failure is elevation of the serum TSH concentration[13-15]. This is illustrated in Figure 1. In the absence of elevated serum TSH, a lesion in the thyroid gland alone is insufficient explanation for presence of the hypothyroid state. Conversely, in man elevation of the serum TSH occurs only, with very rare exceptions, when there is hypothyroidism due to thyroid failure. The exceptions include normal birth, cold exposure in infants, and—extremely

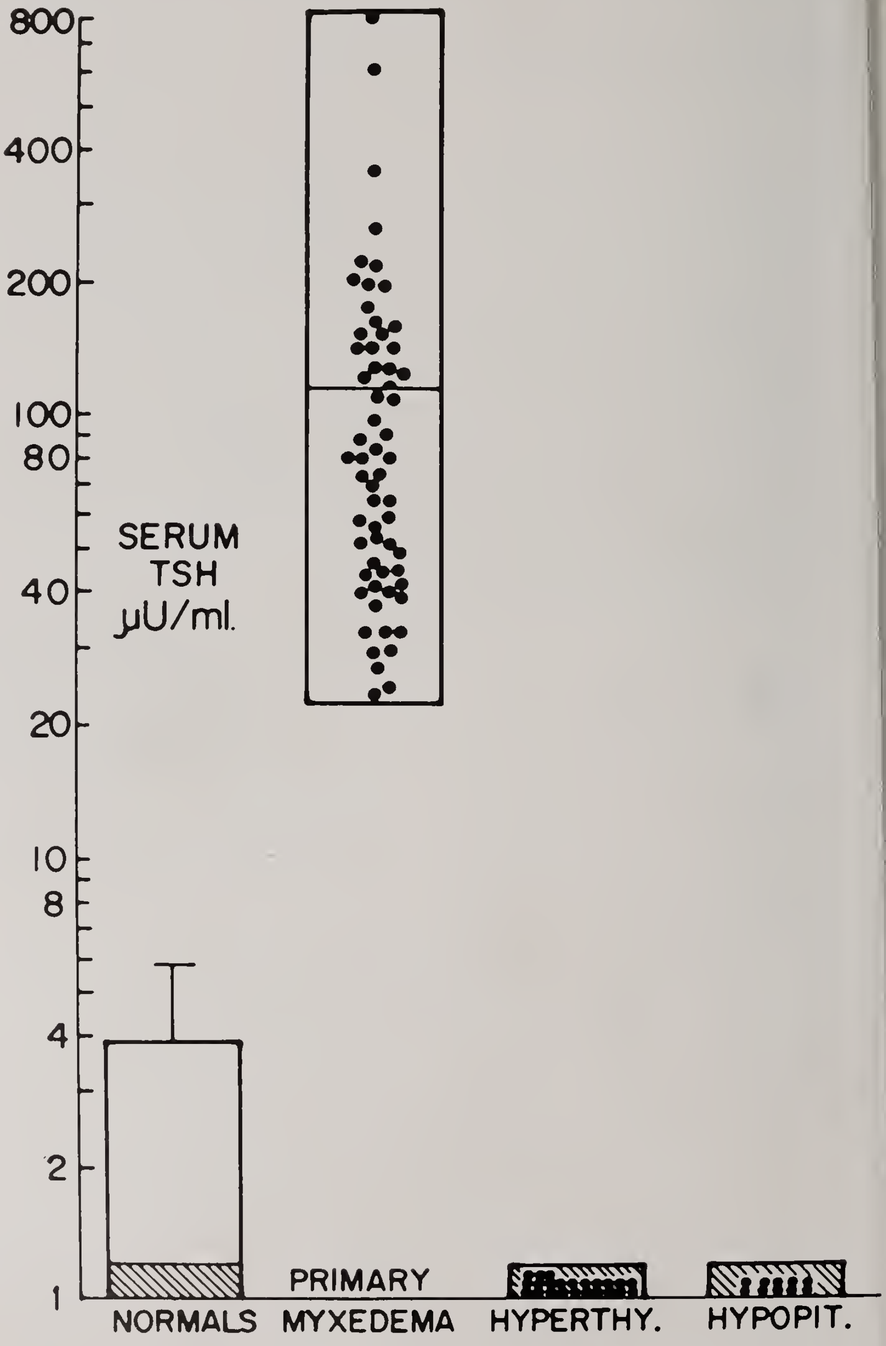

FIG. 1. Serum Thyrotrophin (TSH) in normals (vertical bar shows SD), primary myxedema, hyperthyroidism, and hypothyroidism secondary to hypopituitarism.

rarely–pituitary hypersecretion of TSH with consequent hyperthyroidism. The last named, hypersecretion of TSH, has been documented only in a few patients with pituitary tumors and possibly in one with hypersecretion of hypothalamic TRH (thyrotropin releasing hormone or TRF, (thyrotropin realeasing factor)[16,17]. Normal infants show a transient burst of secretion of TSH by the pituitary with a peak in serum TSH at about one hour of age, after which there is a rapid fall to normal levels over the subsequent day or so[13-15]. This rise does not appear to depend on cold exposure or transient mild hypothermia. However, marked hypothermia such as that used for cardiac surgery can raise serum TSH markedly in subjects up to the age of about two years[18], a response that is lost in adults[19,20]. Thus, elevated serum TSH is a marker for thyroidal hypothyroidism and a laboratory finding virtually pathognomonic for that disease.

Whether or not patients who appear euthyroid but have elevated serum TSH levels are, in fact, hypothyroid is a matter of semantics in part. However, the pituitary obviously is functioning beyond normal limits in such circumstances (e.g., condition of extreme iodine deprivation or postradioiodine therapy for hyperthyroidism); the thyroid gland may be unable to respond to exogenous TSH; and such patients deserve treatment. Therefore, it seems reasonable to consider such individuals with elevated serum TSH values as hypothyroid.

On the other hand, patients with clinical and laboratory evidence of hypothyroidism who have low levels of serum TSH clearly have an inadequate pituitary response to the hypothyroidism, the situation typical of pituitary (or "secondary") hypothyroidism. The designations "primary" and "secondary" seem obsolete and potentially confusing, especially now that "tertiary" (hypothalamic) and other varieties of hypothyroidism are postulated. It is preferable to simply designate the site of the basic lesion.

When referred a patient with hypothyroidism, diabetes insipidus, and short stature, but no evidence of pituitary disease by skull X-rays or visual field examinations and persistently low serum TSH levels, I wondered whether he might not be suffering from a lesion not of the pituitary but of the hypothalamus. Fortunately, it was possible to test this postulate by administration of TRH or TRF. The patient's serum TSH level showed a brisk rise after administration of this hypothalamic hormone, demonstrating a normally responsive pituitary gland and supporting the postulated hypothalamic defect[21]. He thus became "the first case of hypothalamic hypothyroidism reported in a medical journal." The priority claim must be so qualified, however, because Costom, Grumbach, and Kaplan had previously studied patients with short stature and hypothyroidism but no apparent pituitary defects, and they had made similar observations. Their elegant studies appeared shortly after our case report[22] and had been previously reported in abstract. In any case, it is now accepted that lesions in this third site, the hypothalamus, can cause hypothyroidism in patients with intact, though perhaps dormant and hypotrophic, pituitary and thyroid glands. A number of such patients have now been reported[23-26].

The final category listed in Table 1, "Peripheral Hypothyroidism," is less well worked out than the others, primarily because the patients have not been clearly hypothyroid at the time they were studied by Refetoff, DeGroot, *et al*[27,28]. However, x-ray showed the patients to have stippled femoral epiphyses characteristic of infantile hypothyroidism. The patients also showed elevated serum TSH values, goiters, and deficient responses to exogenous thyroid hormone administration. The permanent nerve deafness of the siblings was apparently not the result of the hypothyroidism but a concomitant defect. The basic lesion in these patients has been postulated as in the peripheral (i.e., extra-endocrine) tissues in general, perhaps due to defective tissue receptors for thyroid hormones. A few somewhat similar cases had been described in the past but had not been well documented.

Thyroidal hypothyroidism, as mentioned earlier, accounts for the vast majority of cases of hypothyroidism[1]. Probably about half of these result from destruction of the thyroid gland by the presumably autoimmune process which appears morphologically as Hashimoto's thyroiditis (lymphomatous thyroiditis, or lymphadenoid goiter). Since hyperthyroidism is a more frequent disease in man than hypothyroidism–perhaps about eight times as common–the high rate of thyroidal failure following radioiodine treatment of hyperthyroidism, together with the variable but somewhat lower frequency following surgery, probably accounts for about half of all cases of thyroidal hypothyroidism. These two causes result in overall loss of mass of thyroid tissue with inadequate quantity remaining to secrete normal amounts of thyroid hormones. Together they account for most instances of thyroidal hypothyroidism.

Cryptothyroidism is a term coined by our group in 1965 to describe arrested descent of the embryonic thyroid anlage[29]. Previously, descriptions of the thyroid lesion of cretins which one could find in pathology texts often confused the findings of Hashimoto's thyroiditis with those of cryptothyroidism and sporadic athyreotic cretinism. It had long been known that patients with lingual thyroids sometimes became hypothyroid despite persistence of tissue at the base of the tongue, and Means had suggested that the lesion in such patients resembled cryptorchidism in its pathogenesis[30]. However, "athyreotic" cretinism had been attributed to intrauterine destruction of normally descended fetal thyroid by a process similar to that responsible for Hashimoto's thyroiditis in the adult. Demonstration that most of these patients had small nests of thyroid cells at the base of the tongue, detectable on careful scintiscanning but not otherwise evident, showed that the pathogenesis of sporadic athyreotic cretinism was fundamentally the same as that leading to lingual thyroids but more severe in degree[29].

While there is little doubt that the site of the lesion in cryptothyroidism is the thyroid gland itself, the nature of the deficiency is not well understood. It remains possible that the maldescent (or dysgenesis as McGirr & Hutchison call it) has an autoimmune basis, though this seems unlikely. It also remains possible that there is a concomitant metabolic block in some patients with lingual thyroids and that this accounts for the occurrence of hypothyroidism despite persistence of palpable thyroid tissue. However, such metabolic derangements have never been found when they have been sought in these patients.

Varieties of metabolic blockade leading to hypothyroidism have been thoroughly reviewed elsewhere and will not be discussed here[31]. The genetic defects are rare, some of which are known from only a single reported case[32]. Metabolic blockade from drugs is generally reversible, while that from genetic defects is not.

Hypothalamic hypothyroidism apparently may result from a variety of lesions, such as trauma, tumors (e.g., craniopharyngioma), and perhaps drugs[2,21-26,33]. It has been thought that dexamethasone suppresses TSH by acting purely at the level of the hypothalamus[34], and that "corticogenic hypothyroidism" said to occur in patients receiving long-term treatment with glucocorticoids may result from such an action[2]. However, recent evidence indicates that these steroids can also act at the pituitary to inhibit TSH secretion[34]. In any case, reversible hypothyroidism has occurred in one patient with hypothalamis hypothyroidism[35]. He had a germinoma of the pineal, no lesion in thy region of the hypothalamuc or pituitary, and disappearance of the untreated hypothyroidism following successful irradiation of the tumor.

Patients with hypothalamic hypothyroidism may lack various combinations of other pituitary hormones or neurohormones in addition to TSH[21,22,24]. Presumably this results from impaired secretion of other hypothalamic hormones, such as growth hormone-releasing hormone, luteinizing hormone-releasing hormone, and so on.

Treatment

Treatment of any of these disorders should logically be aimed at correcting the basic lesion insofar as possible. Thus, one would like to remove the pituitary lesion when this is a tumor, or restore hypothalamic function when possible; e.g., by radiating a tumor affecting hypothalamic function. But from a practical viewpoint, we are still restricted in most instances to simply restoring the target glands' hormones, since these are the only ones readily available. But these are generally satisfactory, and patients with hypothyroidism remain among the most satisfying in all medicine to treat, because the treatment is so nearly completely effective in restoring the patient's health.

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Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American Pharmaceutical Association

"Too many doctors are indiffe ent to the economic consequences their decisions." So stated a recent issue of *Medical News Report* (December 4, 1972), an independent weekly newsletter published by forr AMA Chief Executive F. J. L. Blasin game, M.D.

Doctor, are you indifferent...?

In discussing an anticipated i crease in Blue Shield rates, Dr. Bla ingame's newsletter had this to say

"In general, it can be said, MD have given the impression they are not particularly concerned with the increase in cost of health care to th patients...

"True, an MD's training is primarily scientific, but in the real wor of practice, all of his scientific decisions have a price tag, or an econor impact. The economics of health ca beckon the practitioner's attention. Concern for economics of medicine

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical Manufacturers Association

When the pharmacist recommends that a drug product other th the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is nece sary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, th unilateral decision of the pharmacis made in the absence of clinical know edge of the patient, could expose hi to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothi in the pro-substitution argument tha offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowledg about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degre puts him at a disadvantage. Most often, a practicing physician will nee expert knowledge of no more than 2

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d be an obligation of medical ice...

"Medical societies ought to con- continuing campaigns to point e substantial savings that could alized thru deductible insurance rotection for catastrophic ill- At the very least, they should, in atients' interest, question the s of any insurance organization aises health care costs by forc- olicyholders to buy insurance may not need or want and prob- won't ever use.

"Too many doctors are indiffer- o the economic consequences of decisions. Too many, for ex- e, habitually hospitalize patients e convenience of the MD. It's ense to deny such habits exist...

"Doctors, thru their medical so- es, have unhesitatingly appealed eir patients for support in the against government interference the private practice of medicine. the public in the past has re- ded. It's time the American Med- Association and state and local ical societies paid off the debt by sive action to hold down the cost edical care."

of Drugs

Insurance rates and hospital ges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned.* Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

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0 drugs that he selects to treat the ority of conditions encountered in practice. Moreover, the physi- 's choice of a specific brand is ed on his knowledge of the pa- t's medical history and current dition, and his experiences with particular manufacturer's duct.

Some substitution proponents e argued that the dispensing of a scription is a simple two-party saction between the pharmacist the patient, and that a substitut- pharmacist may avoid even a nical breach of contract by simply ifying the patient that he is making substitution. I would judge that courts would be sympathetic ard a pharmacist who substituted hout physician approval and who dertook a legal defense that seeks make the patient responsible for pharmacist's actions.

luced Prescription Prices?

Substitution advocates are gesting to the consumer, and par- ularly the consumer activist, that luced prescription prices could ow legalization of substitution. have seen absolutely no evidence ustify this claim. To the contrary, erience in Alberta, Canada, where ostitution is authorized, suggests the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands—of, say, ampicillin or tetracycline—or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

Pharmaceutical
Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

P·M·A

PRESCRIBING INFORMATION

Antiminth (pyrantel pamoate) Oral Suspension

Actions. Antiminth (pyrantel pamoate) has demonstrated anthelmintic activity against *Enterobius vermicularis* (pinworm) and *Ascaris lumbricoides* (roundworm). The anthelmintic action is probably due to the neuromuscular blocking property of the drug.

Antiminth is partially absorbed after an oral dose. Plasma levels of unchanged drug are low. Peak levels (0.05-0.13μg/ml.) are reached in 1-3 hours. Quantities greater than 50% of administered drug are excreted in feces as the unchanged form, whereas only 7% or less of the dose is found in urine as the unchanged form of the drug and its metabolites.

Indications. For the treatment of ascariasis (roundworm infection) and enterobiasis (pinworm infection).

Warnings. *Usage in Pregnancy:* Reproduction studies have been performed in animals and there was no evidence of propensity for harm to the fetus. The relevance to the human is not known.

There is no experience in pregnant women who have received this drug.

Precautions. Minor transient elevations of SGOT have occurred in a small percentage of patients. Therefore, this drug should be used with caution in patients with pre-existing liver dysfunction.

Adverse Reactions. The most frequently encountered adverse reactions are related to the gastrointestinal system.

Gastrointestinal and hepatic reactions: anorexia, nausea, vomiting, gastralgia, abdominal cramps, diarrhea and tenesmus, transient elevation of SGOT.

CNS reactions: headache, dizziness, drowsiness, and insomnia. Skin reactions: rashes.

Dosage and Administration. *Children and Adults:* Antiminth Oral Suspension (50 mg. of pyrantel base/ml.) should be administered in a single dose of 11 mg. of pyrantel base per kg. of body weight (or 5 mg./lb.); maximum total dose 1 gram. This corresponds to a simplified dosage regimen of 1 cc. of Antiminth per 10 lb. of body weight. (One teaspoonful = 5 cc.)

Antiminth (pyrantel pamoate) Oral Suspension may be administered without regard to ingestion of food or time of day; and purging is not necessary prior to, during, or after therapy. It may be taken with milk or fruit juices. Because of limited data on repeated doses, no recommendations can be made.

How Supplied. Antiminth is available as a pleasant tasting caramel-flavored suspension which contains the equivalent of 50 mg. pyrantel base per ml., supplied in 60 cc. bottles.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

Clean sweep

PINWORMS 0
ROUNDWORMS 0
STAINS 0
ARTHUR

with a single dose of Antiminth
(pyrantel pamoate) ORAL SUSPENSION

Highly effective against pinworm and roundworm

Non-staining to teeth or oral mucosa on ingestion, to stools, clothing, linen

Simple dosage with a single-dose regimen: 1 cc. per 10-lb. body weight (1 tsp./50 lb.; maximum dose, 4 tsp.)

Well-tolerated, based on clinical studies*

Pleasant-tasting, easy-to-take, caramel-flavored oral suspension

Economical, because one prescription can treat the entire family

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

ANTIMINTH®
(pyrantel pamoate)

equivalent to 50 mg. pyrantel/ml.
ORAL SUSPENSION

While Antiminth is highly effective against pinworms and roundworms, the illustration is not meant to imply 100% efficacy.

*Data on file at Roerig.

Please see prescribing information on facing page.

Everybody experiences psychic tension.

Most people can handle this tension.

Some people develop excessive psychic tension and need your counseling

and a few may need counseling
and the psychotropic action of Valium® (diazepam).

Before deciding to make Valium
azepam) part of your treatment
ın, check on whether or not the
tient is presently taking drugs
d, if so, what his response has
en. Along with the medical and
cial history, this information can
lp you determine initial dosage,
e possibility of side effects and
e ultimate prospects of success
failure.

While Valium can be a most
lpful adjunct to your counseling,
should be prescribed only as long
excessive psychic tension per-
sts and should be discontinued
hen you decide it has accom-
ished its therapeutic task. In
neral, when dosage guidelines
e followed, Valium is well
lerated (see Dosage). For con-
nience it is available in 2-mg, 5-mg
d 10-mg tablets.

Drowsiness, fatigue and ataxia
ve been the most commonly re-
rted side effects.

Until response is determined,
tients receiving Valium should
cautioned against engaging in
zardous occupations requiring
mplete mental alertness, such
driving or operating machinery.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 1000.

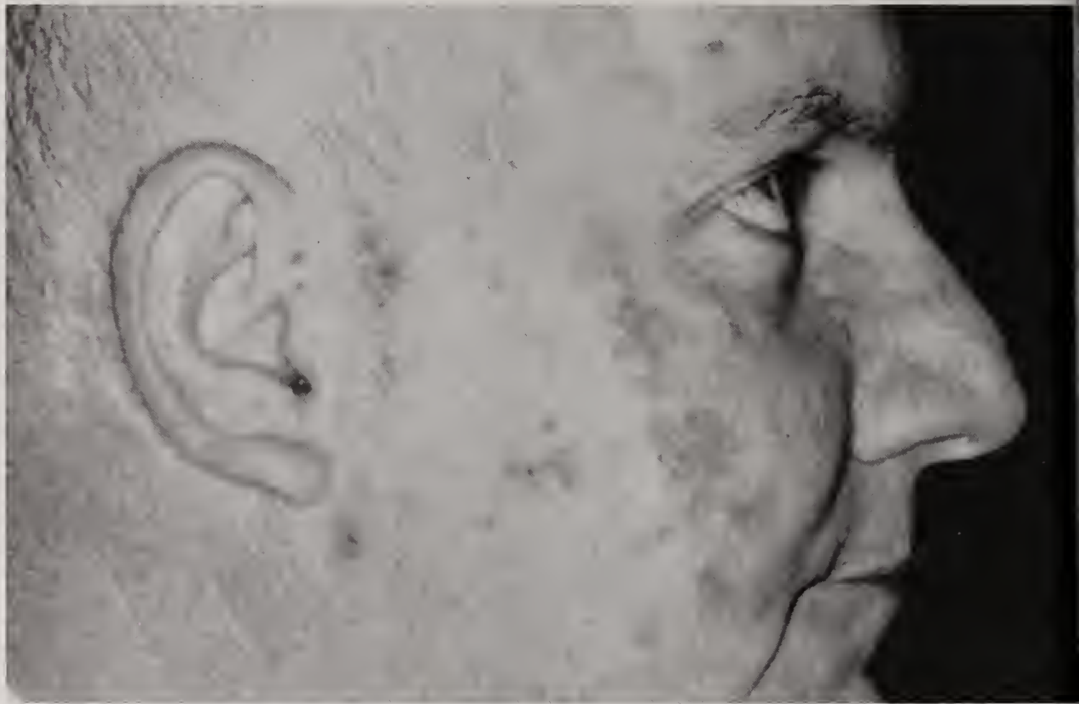
Valium®
(diazepam)

To help you manage excessive psychic tension

What's on your patient's face...

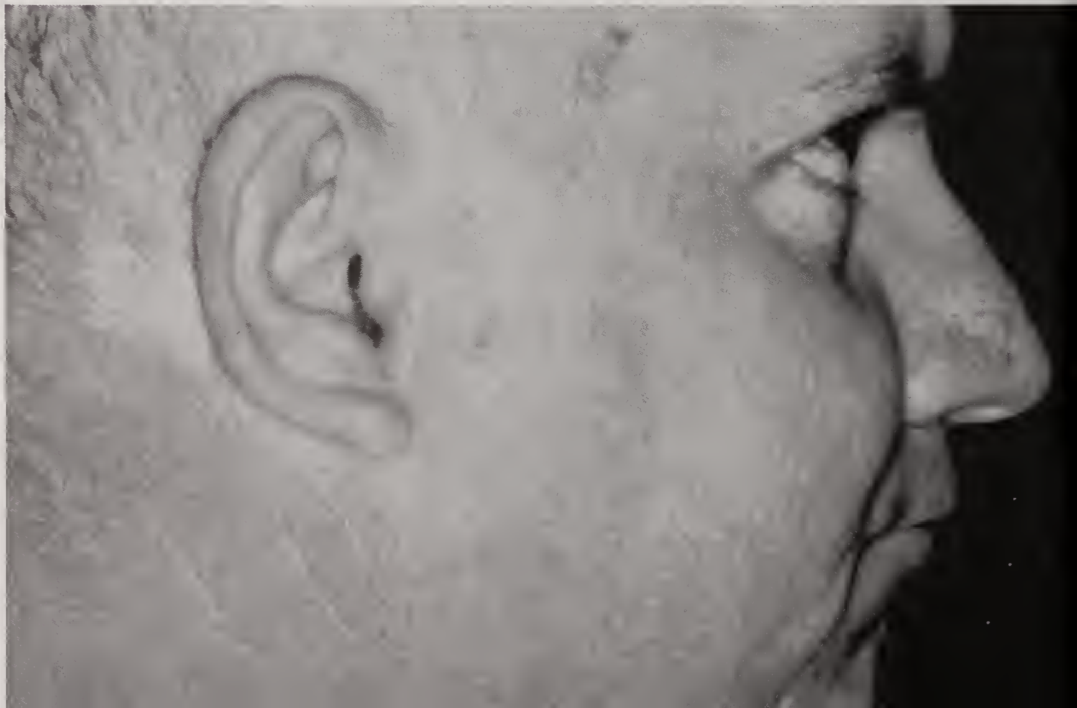
may be more important than his chief complaint

Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.



Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.

*Data on file, Hoffmann - La Roche Inc., Nutley, N.J



The lesions on his face re solar/actinic— o-called "senile" keratoses... nd they may be premalignant.

olar, actinic or senile keratoses

ese lesions may be called by several names, but they
ally can be identified by the following characteris-
s. The typical lesion is flat or slightly elevated, of a
wnish or reddish color, papular, dry, rough, adherent
d sharply defined. They commonly occur as multiple
ions, chiefly on the exposed portions of the skin.

equence of therapy— lectivity of response

ter several days of therapy with Efudex® (fluorouracil),
thema may begin to appear in the area of the lesions;
is reaction usually reaches its height of unsightliness
d discomfort within two weeks, declining after dis-
ntinuation of therapy. This reaction occurs in affected
eas. Since the response is so predictable, lesions that
not respond should be biopsied.

cceptable results

eatment with Efudex provides highly favorable cos-
tic results. Incidence of scarring is low. This is par-
ularly important with multiple facial lesions. Efudex
ould be applied with care near the eyes, nose and mouth.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.

Contraindications: Patients with known hypersensitivity to any of its components.

Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)-aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

This patient's lesions were resolved with Efudex® fluorouracil/Roche®

5% cream/solution...a Roche exclusive

The Rx that says "Relax"

BUTISOL Sodium provides highly predictable sedative effect: minor dosage adjustments are usually all that's needed to produce the desired degree of sedation. (With 3 dosage forms and 4 strengths to make adjustments easy.)

BUTISOL Sodium offers prompt, smooth, relatively non-cumulative action: begins to work within 30 minutes...yet, because of its intermediate rate of metabolism, generally has neither a "roller-coaster" nor a "hangover" effect.

BUTISOL Sodium is remarkably well tolerated: a 30-year safety record assures you that there is little likelihood of unexpected reactions.

BUTISOL Sodium saves your patients money: costs less than half as much as most commonly prescribed sedative tranquilizers.*

These are four good reasons for prescribing BUTISOL Sodium for the many patients who need to have the pace set just a little slower. Its gentle daytime sedative action is often all that's needed to help the usually well-adjusted patient cope with temporary stress.

*Based on surveys of average daily prescription costs.

Butisol SODIUM®
(SODIUM BUTABARBITAL)

Contraindications: Porphyria, sensitivity to barbiturates, or susceptibility to dependence on sedative-hypnotics. **Warning:** May be habit forming. **Precautions:** Exercise caution in: moderate to severe hepatic disease; withdrawal in drug dependence or the taking of excessive doses over a long period, to avoid withdrawal symptoms; elderly or debilitated patients, to avoid possible marked excitement or depression; use with alcohol or other CNS depressants, because of combined effects. **Adverse Reactions:** Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and gastrointestinal disturbances are seldom seen. **Usual Adult Dosage:** For daytime sedation, 15 mg. to 30 mg. t.i.d. or q.i.d. For hypnosis, 50 mg. to 100 mg. **Available as:** Tablets, 15 mg., 30 mg., 50 mg., 100 mg.; Elixir, 30 mg. per 5 cc. (alcohol 7%). BUTICAPS® [Capsules BUTISOL SODIUM (sodium butabarbital)] 15 mg., 30 mg., 50 mg., 100 mg.

McNEIL McNeil Laboratories, Inc., Fort Washington, Pa. 19034

IN ASTHMA
IN EMPHYSEMA

optional therapy

*

THE **mudranes**®

All Mudranes are bronchodilator-mucolytic in action, and are indicated for symptomatic relief of bronchial asthma, emphysema, bronchiectasis and chronic bronchitis. **MUDRANE tablets** contain 195 mg. potassium iodide; 130 mg. aminophylline; 21 mg. phenobarbital (Warning: may be habit-forming); 16 mg. ephedrine HCl. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline-phenobarbital-ephedrine combinations. **Iodide side-effects:** May cause nausea. Very long use may cause goiter. Discontinue if symptoms of iodism develop. **Iodide contraindications:** Tuberculosis; pregnancy (to protect the fetus against possible depression of thyroid activity). **MUDRANE-2 tablets** contain 195 mg. potassium iodide; 130 mg. aminophylline. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline. **Iodide side-effects and contraindications are listed above. MUDRANE GG tablets** contain 100 mg. glyceryl guaiacolate; 130 mg. aminophylline; 21 mg. phenobarbital (Warning: may be habit-forming); 16 mg. ephedrine HCl. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions** are those for aminophylline-phenobarbital-ephedrine combinations. **MUDRANE GG-2 tablets** contain 100 mg. glyceryl guaiacolate; 130 mg. aminophylline. **Dosage** is one tablet with full glass of water, 3 or 4 times a day. **Precautions:** Those for aminophylline. **MUDRANE GG Elixir.** Each teaspoonful (5 cc) contains 26 mg. glyceryl guaiacolate; 20 mg. theophylline; 5.4 mg. phenobarbital (Warning: may be habit-forming); 4 mg. ephedrine HCl. **Dosage:** Children, 1 cc for each 10 lbs. of body weight; one teaspoonful (5 cc) for a 50 lb. child. Dose may be repeated 3 or 4 times a day. Adult, one tablespoonful, 4 times daily. All doses should be followed with ½ to full glass of water. **Precautions:** See those listed above for Mudrane GG tablets.

MUDRANE—original formula
First choice

MUDRANE-2
When ephedrine is too exciting
or is contraindicated

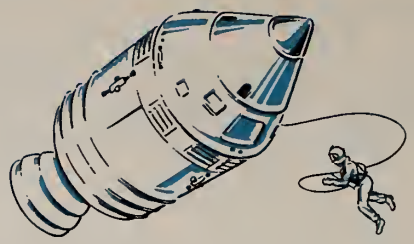
MUDRANE GG
During pregnancy or when K.I. is
contraindicated or not tolerated

MUDRANE GG-2
A counterpart for Mudrane-2

MUDRANE GG ELIXIR
For pediatric use
or where liquids are preferred

Clinical specimens
available to physicians.

WILLIAM P. POYTHRESS & COMPANY, INC., RICHMOND, VIRGINIA 23217
Manufacturers of Ethical Pharmaceuticals



Man in space, now fait accompli, re-emphasizes the importance of Uro-Phosphate therapy. Research into the effect of space travel on the astronaut reveals that weightlessness causes loss of bone calcium. As the bones are required to bear less and less of the weight of the body they lose calcium, increasing the calcium content of the urine. When physical activity is reduced, the acidity of the urine should be adjusted to keep increased calcium in solution . . . . a prophylaxis to prevent kidney or bladder calculi.

Uro-Phosphate®

NOW A SUGAR-COATED TABLET

Each tablet contains: METHENAMINE, 300 mg.; SODIUM ACID PHOSPHATE, 500 mg.

Uro-Phosphate gives comfort and protection when inactivity causes discomfort in the urinary function. It keeps calcium in solution, preventing calculi; it maintains clear, acid, sterile urine; it encourages complete voiding and lessens frequency when residual urine is present.

Uro-Phosphate contains sodium acid phosphate, a natural urinary acidifier. This component is fortified with methenamine which is inert until it reaches the acid urinary bladder. In this environment it releases a mild antiseptic keeping the urine sterile.

Uro-Phosphate is safe for continuous use. There are no contra-indications other than acidosis. It can be given in sufficient amount to keep the urine clear, acid and sterile. A heavy sugar coating protects its potency.

Dosage:

For protection of the inactive patient 1 or 2 tablets every 4 to 6 hours is usually sufficient to keep the urine clear, acid and sterile.

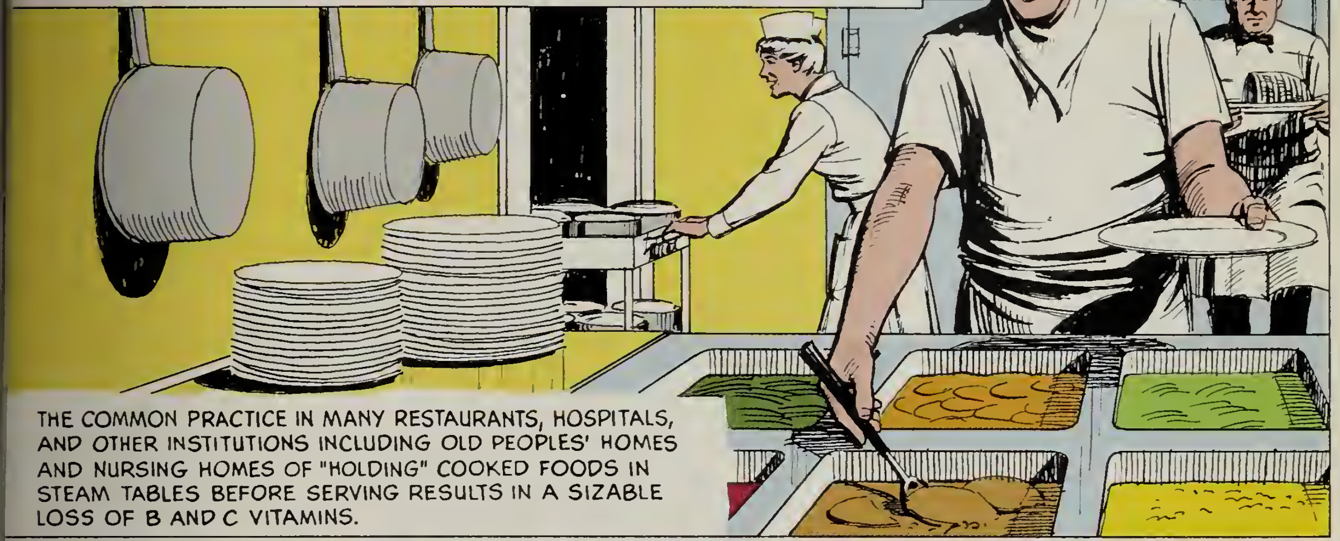
2 tablets on retiring will keep residual urine acid and sterile, contributing to comfort and rest.

A clinical supply will be sent to physicians and hospitals on request.

WILLIAM P. POYTHRESS & COMPANY, INC., RICHMOND, VIRGINIA 23217

Manufacturers of Ethical Pharmaceuticals

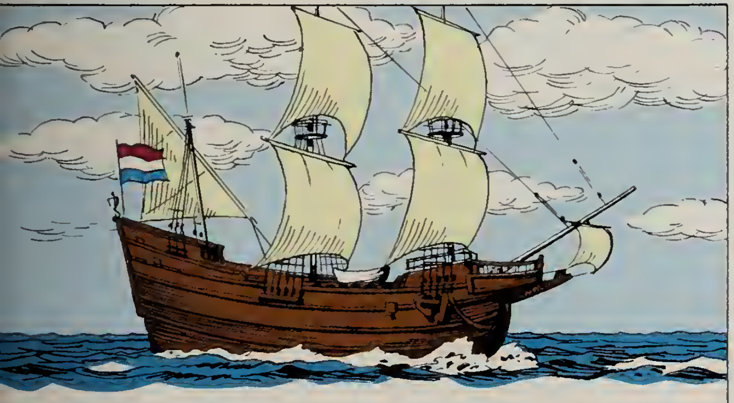
he ALLBEE® with C SCRAPBOOK of Vitamin Facts & Fallacies



THE COMMON PRACTICE IN MANY RESTAURANTS, HOSPITALS, AND OTHER INSTITUTIONS INCLUDING OLD PEOPLES' HOMES AND NURSING HOMES OF "HOLDING" COOKED FOODS IN STEAM TABLES BEFORE SERVING RESULTS IN A SIZABLE LOSS OF B AND C VITAMINS.

DURING THE CIVIL WAR 30,714 CASES OF SCURVY WERE REPORTED, AND 383 DEATHS WERE ATTRIBUTED DIRECTLY TO THE DISEASE.

THE AMOUNT OF SUNLIGHT AVAILABLE DURING RIPENING DETERMINES TO A LARGE EXTENT THE FINAL ASCORBIC ACID CONTENT OF TOMATOES. HENCE, A COOL, WET SUMMER PRODUCES WATERY, LESS TASTY FRUIT THAT'S LOWER IN VITAMIN C.



RONSSENS, A DUTCH PHYSICIAN, WROTE IN 1564 THAT "DUTCH SAILORS WHO, RETURNING FROM SPAIN, WERE ATTRACTED BY THE NOVEL RICHNESS OF THE FRUIT (ORANGES) AND BY THEIR GREED AND GLUTTONY, UNEXPECTEDLY DROVE OUT THE DISEASE (SCURVY), AND HAD THIS HAPPY EXPERIENCE NOT ON A SINGLE OCCASION ONLY, BUT REPEATEDLY."

Available on your prescription or recommendation

ALLBEE® with C

High Potency B-Complex and Vitamin C Formula

AHR
Allbee® with C
MULTIVITAMINS
Each capsule contains % MDR
Thiamine mononitrate (B₁) 15 mg 1500%
Riboflavin (B₂) 10 mg 834%
Pyridoxine hydrochloride (B₆) 5 mg *
Niacinamide 50 mg 500%
Calcium pantothenate 10 mg **
Ascorbic acid (Vitamin C) 300 mg 1000%
30 CAPSULES
A·H·ROBINS
AHR

A.H. Robins Company, Richmond, Va. 23220 A·H·ROBINS

Spasm reactor?
Donnatal!

	each tablet, capsule or 5 cc. teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg.
atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg.
hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg.
(warning: may be habit forming)			

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

A·H·ROBINS A H Robins Company. Richmond. Virginia 23220

He won't resist feeling better with Mylanta®

Because the taste is good.

- ☐ promptly relieves hyperacidity
- ☐ also relieves fullness and bloating
- ☐ non-constipating

LIQUID **MYLANTA®** TABLETS

aluminum and magnesium hydroxides with simethicone

STUART PHARMACEUTICALS | Division of ICI America Inc. | Wilmington, Del. 19899 | Pasadena, Calif. 91109

“Antiacid” action for ulcer patients…

one of the many things you need in an anticholinergic.

Pro-Banthīne is provided in several different dosage forms and combinations which will meet virtually any clinical need. It is just as versatile in filling patient needs, among which are:

"Antiacid" action—Pro-Banthīne® (propantheline bromide) reduces gastric secretory volume and resting total and free acid.

"Sustained" action—Pro-Banthīne P.A.® (propantheline bromide) contains 30 mg. of the drug in the form of sustained-release or timed-release beads; on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metabolized.

High-level anticholinergic activity is maintained all day and all night in most patients with only two tablets every eight hours.

"Analgesic" action—Pro-Banthīne helps to control the acid-spasm-pain complex.

A "diagnostic tool"—Pro-Banthīne may be used parenterally to immobilize the duodenum for more revealing roentgenographic appraisal through hypotonic duodenography.

Pro-Banthīne is considered adjunctive in total peptic ulcer therapy that may include diet, conventional antacids, bed rest, and other supportive measures.

Vigorous anticholinergic action — Pro-Banthīne® Vials, 30 mg., are for intramuscular or intravenous use when prompt and vigorous anticholinergic action is required.

Mild anticholinergic action—Pro-Banthīne® Half Strength, 7.5-mg. tablets, for more exact adjustment of maintenance dosage in mild to moderate gastrointestinal disorders.

Indications: Pro-Banthīne is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution.

Fever and possibly heat stroke may occur due to anhidrosis.

In theory a curare-like action may occur, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted.

Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthīne.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may occur as well as mydriasis and blurred vision. In addition the following adverse reactions have been reported: nervousness, drowsiness, dizziness, insomnia, headache, loss of the sense of taste, nausea, vomiting, constipation, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult oral therapy is one 15-mg. tablet with meals and two at bedtime. Subsequent adjustment to the patient's requirements and tolerance must be made.

Pro-Banthīne P.A.—Each tablet of Pro-Banthīne P.A. (propantheline bromide) contains 30 mg. of the drug in the form of sustained-release or timed-release beads; on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metabolized. Thus the result is even, high-level anticholinergic activity maintained all day and all night in most patients with only two tablets daily. Some patients may require one tablet every eight hours.

The contraindications and precautions applicable to Pro-Banthīne 15 mg. should be observed.

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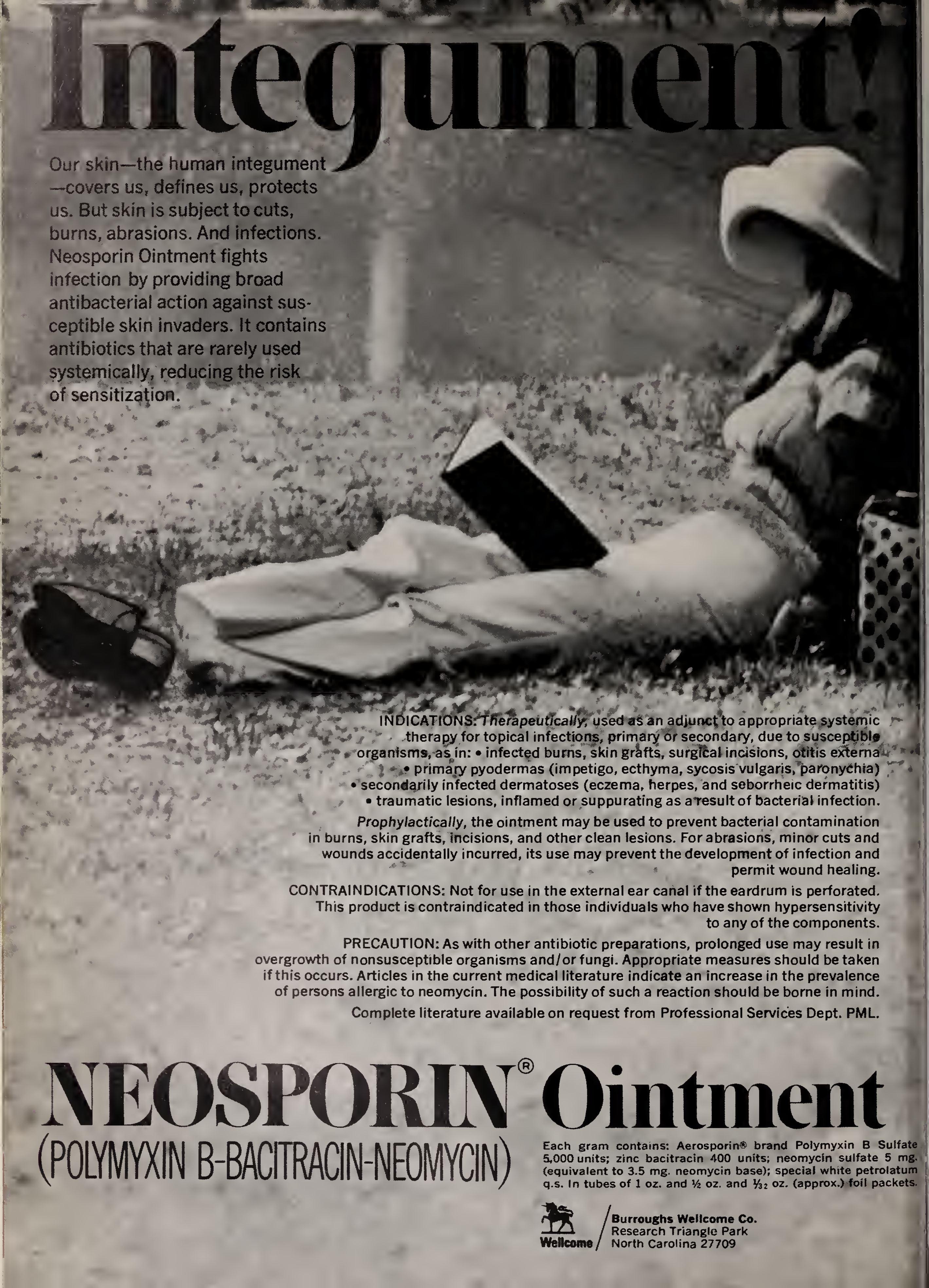
a good option in peptic ulcer



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INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

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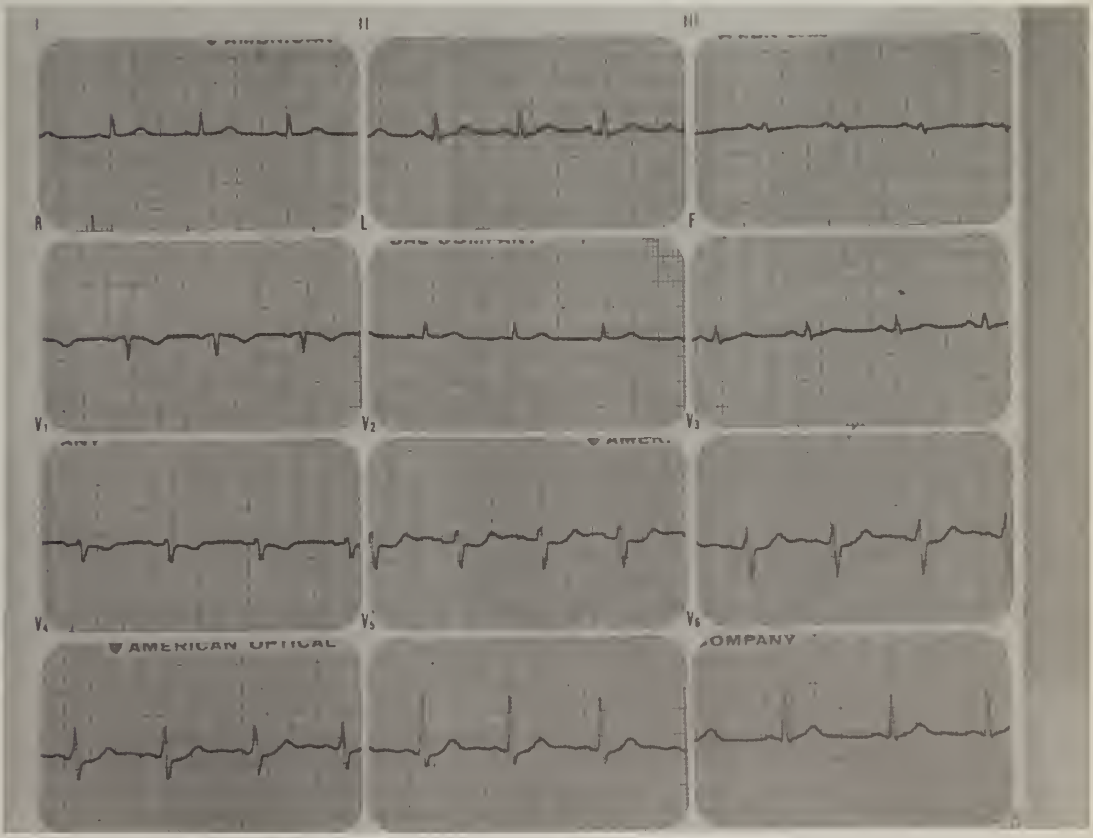
ECG Problems

HISTORY: Severe retrosternal pain beginning while straining at stool on the day of the electrocardiogram #1. Pain radiated to the volar aspect of both forearms and down to the wrists with associated perspiration and moderate dyspnea.

ECG #2 was taken two days later. Pain had disappeared. There was slight fever and typical enzyme changes usually associated with acute myocardial infarction.

ECG #1


I
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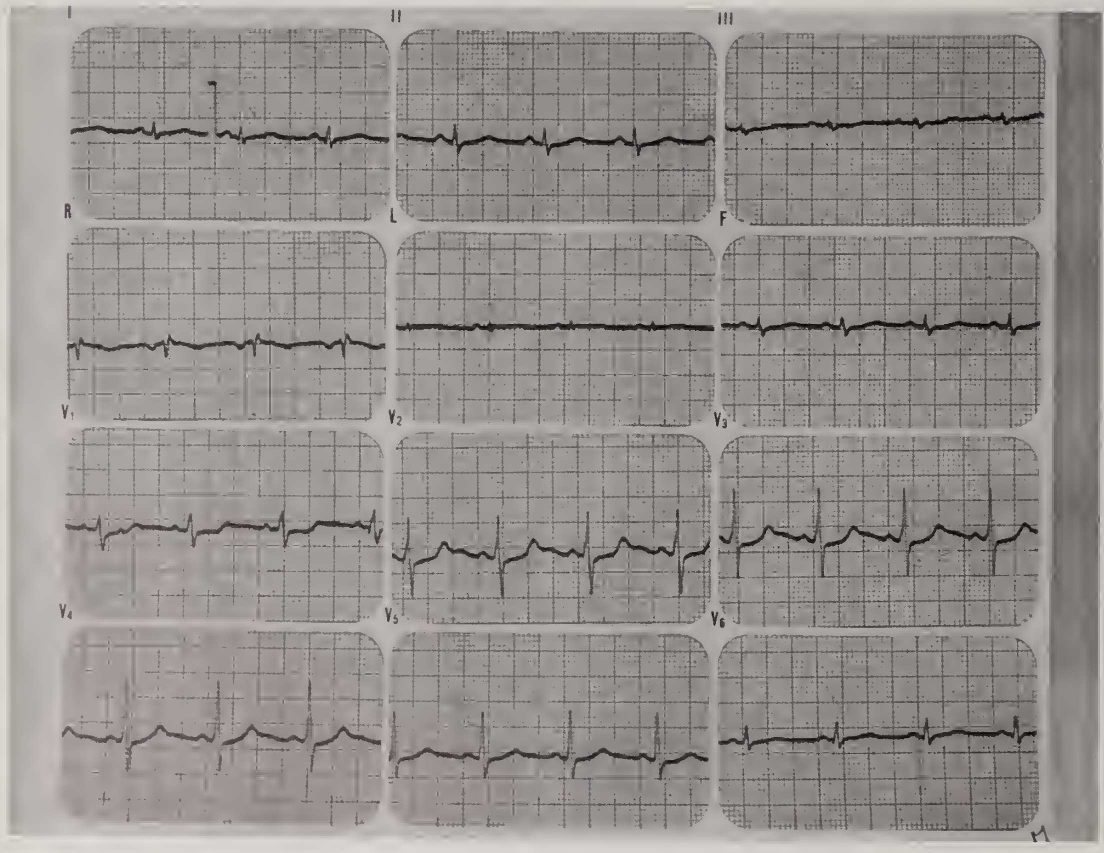
ECG #2


I
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L
F
V1
V2
V3
V4
V5
V6

(For diagnosis see page 472)

NEW MEMBERS

Active

NATHAN BILLIG, M.D. Office: 5225 Connecticut Avenue. Born in New York, New York. Medical degree: S.U.N.Y. Upstate, 1966. Specialty: Psychiatry.

WILBUR CALLENDER, M.D. Office: D.C. General Hospital. Born in St. Thomas, Virgin Islands. Medical degree: Howard University, 1967. Specialty: Obstetrics-Gynecology.

NERITA R. ESTAMPADOR, M.D. Office: Howard University. Born in the Philippines. Medical degree: University of the Philippines, 1963. Specialty: Pediatrics.

CHESTER GEE, M.D. Office: 3901 Georgia Avenue. Born in Milwaukee, Wisconsin. Medical degree: Howard University, 1963. Specialty: Orthopedics.

WILLIAM S. IBRAHIM, M.D. Office: 2121 Pennsylvania Avenue. Born in Egypt. Medical degree: Alexandria University (Egypt), 1958. Specialty: Ophthalmology.

SE DUCK KIM, M.D. Office: 5th & W Street, N.W. Born in Seoul, Korea. Medical degree: Yonsei University, 1962. Specialty: Pathology.

GIDEON KIOKO, M.D. Office: 3211 Pennsylvania Avenue, S.E. Born in Kenya, East Africa. Medical degree: Meharry Medical College, 1969. Specialty: Obstetrics-Gynecology.

MINDA MASSENGALE, M.D. Office: 110 Irving Street, N.W. Born in the Philippines. Medical degree: University of Santo Tomas (Philippines), 1957. Specialty: Anesthesiology.

HENRY B. MARSH, M.D. Office: 110 Irving Street. Born in Washington, D.C. Medical degree: Johns Hopkins, 1966. Specialty: Cardiology.

VIBHAKAR J. MODY, M.D. Office: 1726 Eye Street, N.W. Born in India. Medical degree: Mysore University (India), 1967. Specialty: Obstetrics-Gynecology.

JOHN F. MORETTI, M.D. Office: 1026 16th Street, N.W. Born in Washington, D.C. Medical degree: Georgetown University, 1967. Specialty: Ophthalmology.

PAUL R. MOYER, M.D. Office: 2300 K Street, N.W. Born in Philadelphia, Pa. Medical degree: University of Pennsylvania, 1967. Specialty: Internal Medicine.

LOUIS NAPOLI, M.D. Office: Providence Hospital. Born in New York, New York. Medical degree: Upstate Med. S.U.N.Y., 1967. Specialty: Radiology.

MICHAEL PASSARETTI, M.D. Office: 916 19th Street, N.W. Medical degree: Tufts Medical School, 1968. Specialty: Orthopedic Surgery.

AMIEL SEGAL, M.D. Office: 1100 22nd Street, N.W. Born in Washington, D.C. Medical degree: University of Pennsylvania. Specialty: Internal Medicine–Hematology.

POONG SUP SHIM, M.D. Office: Georgetown University Hospital. Born in Seoul, Korea. Medical degree: Seoul National University (Korea), 1964. Specialty: Nephrology.

ALLEN SMALL, M.D. Office: 1234 19th Street, N.W. Born in Brooklyn, New York. Medical degree: S.U.N.Y. Downstate, 1966. Specialty: Otolaryngology.

JONATHAN D. TUERK, M.D. Office: 2605 Northampton Street, N.W. Born in Baltimore, Maryland. Medical degree: University of Maryland, 1964. Specialty: Psychiatry.

ANTONIO UY, M.D. Office: 6711 New Hampshire Avenue. Born in Philippines. Medical degree: University of East Ramon Magsaysay (Philippines), 1965. Specialty: Internal Medicine.

WILLIAM H. WEINTRAUB, M.D. Office: Children's Hospital. Born in New Rochelle, New York. Medical degree: Harvard University, 1964. Specialty: Pediatric Surgery.

Associate

ARTHUR KANE, M.D. Office: 3611 Branch Avenue. Born in New York, New York. Medical degree: Georgetown University, 1969. Specialty: Obstetrics-Gynecology.

ELIZABETH KULTCHAR, M.D. Office: Malcolm Grow Medical Center. Born in Chicago, Illinois. Medical degree: Medical College of Pennsylvania, 1959. Specialty: Pediatrics.

JEAN C. PILET, M.D. Office: PO Box 822, Silver Spring, Maryland. Born in Haiti. Medical degree: U. School of Medicine & Pharmacy of Haiti. Specialty: Ophthalmology.

Resident-Intern

JOSEPH ADOLPH, M.D. Office: Georgetown Hospital. Born in Boston, Massachusetts. Medical degree: Tufts University, 1970. Specialty: Urology.

JULIAN LOUBE, M.D. Office: George Washington University Medical Center. Born in Washington, D.C. Medical degree: George Washington University, 1972. Specialty: Obstetrics-Gynecology.

ALEJANDRO RIVERA, M.D. Office: Rogers Memorial Hospital. Born in Cabanatuan City, Philippines. Medical degree: University of Santo Tomas (Philippines), 1965. Specialty: Family Practice.

MICHAEL SPEVAK, M.D. Office: Georgetown Hospital. Born in Schenectady, New York. Medical degree: Georgetown University, 1969. Specialty: Child Psychiatry.

BERNARD STOPAK, M.D. Office: George Washington University Hospital. Born in Washington, D.C. Medical degree: Faculte de Medecine (Montpellier, France), 1970. Specialty: Neurosurgical Resident.

Student

Georgetown Medical School. Sophmore: Margaret Stryker.

Changes in Membership

Transfers

Associate to Active: Dara S. Afshar, M.D., Herbert Golomb, M.D.

Resident-Intern to Active: William Elliot, M.D., Melvin D. Gerald, M.D., Barry J. Landau, M.D.

Active to Special: Henry W. Edmonds, M.D., Edna Jeffreys, M.D.

Active to Associate: J. R. Thistlethwaite, M.D.

Reinstatement

Active: Straty Economon, M.D.

Resignations

Active: Robert Marier, M.D.

Associate: Ronald W. Smith, M.D., Donald B. Wheeler, M.D.

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book REVIEWS

Acute Inflammation. J. V. HURLEY, M.D. Price, $14.75. Pp. 137 with illustrations. Baltimore, Maryland: The Williams and Wilkins Company, 1972.

Knowledge of the inflammatory process has increased due to the introduction of new experimental techniques, especially electromicroscopy. Current views on the morphology and mechanisms of inflammation and sequelae are presented.

Following an injury, a reaction involving characteristic changes takes place in the damaged area. These include increased vascular permeability associated with endogenous chemical mediators (proteases, amines), direct destructive changes in the wall (endothelium) of small blood vessels, increased vascular flow of polymorphonuclear cells (leucocytic emigration), and increased fibrin and plasma leakage (protein loss) into extravascular tissues due to differences in hydrostatic pressure within the blood vessels.

The cardinal signs of inflammation summarized by Celsus (30 B.C.-A.D. 38) and in 1882 (Cohnheim's description) are well known, as well as the different types of injury–physical, chemical, bacterial and immunological. Depending on the type of injury and the degree of tissue destruction by the agent, termination of the acute inflammatory reaction and resolution with restoration takes place to complete normal tissue, or subsequently with connective tissue replacement. In those cases with overwhelming infection, death may result.

In "Acute Inflammation," the normal function of polymorphs in the removal of exudate and dead tissue; lymphatic drainage; the importance of rest to the inflamed part as well as cellulitis; suppuration with purulent exudate, ie. polymorphs, microorganisms, killed tissue cells and/or abscess formation; and the role of a foreign body contributing to the persistence of suppuration are discussed. At the end of each chapter is a list of references supporting the text and current views.

Polymorphs participated through release of enzymes and by amoeboid action, particles, cellular debris, or bacteria are engulfed in phagocytic vacuoles.

In addition to the above, in chronic (productive) inflammation, blood monocytes and morophages are present. Aside from the duration of the process, healing, pleomorphic cells, fibroblasts (collagen formation) are distinguishing characteristics. The histological feature of foreign body giant cells, plasma cells, eosinophils and lymphocytes are recognized as essentials in chronic inflammation. The author states that if the variety of cell types in the area of the lesion is free from necrosis, the condition is probably chronic inflammation; if, by contrast, one type cell is present the lesion is probably neoplastic.

Tuberculosis is the most atypical form of chronic inflammation. It may be difficult to make the etiological diagnosis and thus should be confirmed by demonstrating the tubercle bacillis either microscopically or identifying it by culture. It used to be thought that a peripheral ring arrangement of the nuclei of giant cells was characteristic of tuberculosis, and cells of this type were called Langhan's giant cells. However, the distinction is not a valid one, and there is no consistent difference in the arrangement of giant cell nuclei in tuberculosis and the reaction to other types of poorly absorbed material.

Eosinophils are present in both acute and chronic inflammation and react chemotactically to the same substances that attract nutraphil polymorphs. However, eosinophils are the predominate cells in allergic reactions and in certain parasitic infestations, but the specific function of eosinophils is still unknown.

Much has been learned of the behavior and function of lymphocytes during the past ten years. Lymphocytes are not fixed cells and can be immunologically competent cells.

This book is of value to the pathologist, the research worker in pathology, and the surgeon.

JOHN STUBENBORD, M.D.

Your Brain and Nerve. J. LAWRENCE POOL, M.D. Price, $7.95. Pp. 211 with illustrations.

Dr. Pool, Emeritus Professor of Neurological Surgery at Columbia University, explains in the preface that his book's main purpose is to "reduce the natural apprehension that people have regarding the clearly remediable conditions with which neurosurgeons deal." His book, obviously, is addressed to lay people. His method is the capsule presentation of case histories followed by a description of the pathophysiology and the diagnostic and therapeutic techniques pertinent to each case. The text is accompanied by four diagrammatic drawings and by a glossary. In literary style, this book achieves a level somewhere between MacDuffie's Reader and Reader's Digest, which is at least adequate for the quality of the information which is offered. Some statements are meaningless, as "It is often difficult to know whether a person is simply unconscious or in coma . . . the unconscious patient gradually tends to show signs of recovery, whereas the comatose patient does not"; some statements are false, as "Midbrain injury may also lead to . . . even blindness;" and some statements are misleading, as the assertion that "Bell's palsy may be cured by ear surgery" and the assertion that "surgery offers relief" for those patients with disc disease not benefited by conservative treatment. Beyond, and perhaps underlying these shortcomings, is the fundamentally untenable purpose set forth in the preface; it should, rather, be acknowledged that neurosurgeons do *not* deal with clearly remediable conditions, and that there are good reasons for their patients to have apprehension. What should be available to the patient is a clear and realistic explanation of his illness and the proposed treatment. For this purpose there is better material available, including well-written monographs on neurological diseases issued by the National Institute of Neurological Diseases and Stroke.

ELLIOT C. WILNER, M.D.

Understanding Cancer. BRYAN N. BROOKE. Price, $4.95. Pp. 122. New York: Holt, Rinehart & Winston, 1971.

This small volume has been written by an English surgeon to try to clarify the mysteries of cancer for the layman. The author has succeeded in producing an accurate and up-to-date delineation of the facts, in a relatively simple and straightforward manner.

The introduction is marred by a lengthy accusation of the medical profession of secretiveness and noncommunication with patients regarding their illnesses, particularly cancer. Although this may be true in England, it is rapidly becoming an outmoded attitude in the United States.

The remainder of the book presents rather clearly the current facts regarding the cellular basis of life, the factors which relate to cancer, and the present status of diagnosis and treatment. I believe that this book may be recommended to patients with education and intelligence who wish to learn more about cancer than they can from newspapers and magazines.

LOUIS K. ALPERT, M.D.

Essentials of Artificial Ventilation of the Lungs. A. R. HUNTER. Price $7.75. Pp. 95 with illustrations. London, England, and Edinburgh, Scotland: Churchill-Livingstone, 1972.

The title of this short 87-page monograph is misleading since it covers in a very superficial manner, all types of supportive therapy besides artificial ventilation, from the care of tracheostomy, use of ventilators, acid-base balance, fluid therapy, respiratory failure and finally brain death.

The criteria for instituting ventilatory therapy are ill-defined and poor. In two chapters, cyanosis is considered as an essential indication for ventilatory supportive therapy; this may or may not appear, depending on the amount of reduced hemoglobin in the blood. The description of how to manipulate equipment is incomplete and uninformative.

The booklet has a few tidbits that might be helpful, such as some normograms on acid-base balance, importance of sterilizing equipment, the passage of a Ryle's tube and the usual complications encountered with a tracheostomy tube.

Although the author claims complete revision and updating of the manuscript, there are very few recent references quoted.

I do not feel that this book has much to offer as a source of information or as a primer for students, nurses or paramedical personnel involved in artificial ventilation of the lungs.

S. N. ALBERT, M.D.

The Medical Garden. GEOFFREY MARKS AND WILLIAM K. BEATTY. Pp. 178. Price, $2.65. New York: Charles Scribner's Sons, 1971.

The German herb medicine industry is proving an obstacle to Common Market integration. The United States is paying Turkey $35 million not to grow opium; now there is fear of insufficient morphine and codeine for medicinal use. Cocaine, studied by Freud and abused by the great Hopkins surgeon, Halsted, was seized recently in a cache under a load of bananas on the ship, City of Bogota. Heroin "chippers" in Vietnam and elsewhere may get easily unhooked or may turn to alcohol or other central nervous stimulants and depressants as to a circle of crutches.

All the above slices of life today are relevant to Geoffrey Marks' and William K. Beatty's "The Medical Garden". It deals with seven drugs originally derived from plant forms, and is thus reminiscent of "Green Medicine" by Margaret Kreig.

Obviously, botanical medicine is alive and on the march, and scientific "discoveries" often spring from nature's remedies.

Fascinating and serendipitous mishaps and breakthroughs surround the histories of opium, cocaine, quinine, aspirin, colchicine, digitalis and penicillin. All can be useful, but their "misuse, or abuse, is dangerous and sometimes fatal."

What made Mohammed ban alcohol, and not opium or hashish? How did we allow nice nineteenth century ladies to become addicted to opium in Dr. Pierce's Golden Discovery? Physicians habitually laugh at native remedies before employing them wisely. William Withering was an exception. He humbly learned from a patient and an old lady prescriber's "cure for dropsy"; then isolated foxglove as the active principle from the twenty herbs.

This book, written in a clear, engaging style, sticks to the historic and scientific facts with greater dignity and responsibility than "Green Medicine", and can be recommended unreservedly to students and interested scientists and laymen. There are useful references, illustrations, and an index.

ARTHUR RUSKIN, M.D.

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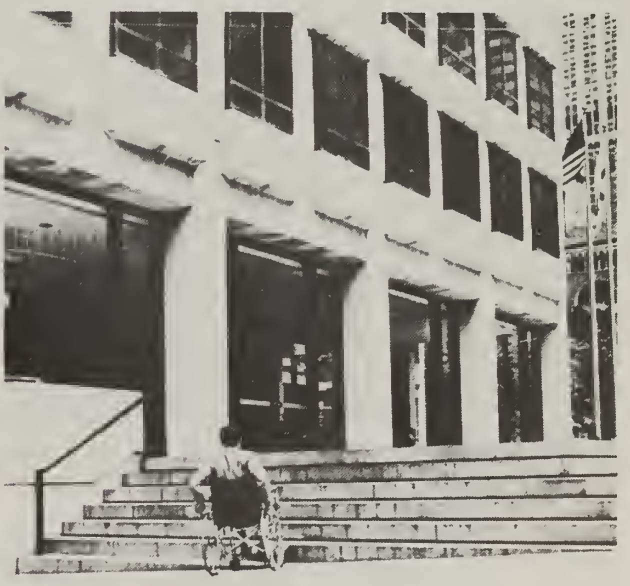

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- Published career materials and established a scholarship loan fund to help recruit future medical assistants.
- Cooperated with AMA in public relations efforts beneficial to the medical profession as a whole.

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Recommendations[†] on Combination Live Virus Vaccines

American Academy of Pediatrics

Committee on Infectious Diseases

In the September 15, 1971 *AAP Newsletter* sent to Academy members, the Committee on Infectious Diseases of the American Academy of Pediatrics stated its recommendations on the use of combination live virus vaccines. After a careful review of available data, the committee concluded that:

- "This information indicates that the products are both safe and effective when used as directed."
- The vaccine "...can, therefore, be recommended with the obvious advantages of reduction in the number of injections for any given child and a concomitant decrease in the required visits to a physician's office or clinic."

United States Public Health Service

Advisory Committee on Immunization Practices

In the April 24, 1971 issue of *Morbidity and Mortality Weekly Report,* the Advisory Committee on Immunization Practices of the United States Public Health Service presented recommendations on the use of combination live virus vaccines. The committee stated that:

- "Data indicate that antibody response to each component of these combination vaccines is comparable with antibody response to the individual vaccines given separately.
- "There is no evidence that adverse reactions to the combined products occur more frequently or are more severe than known reactions to the individual vaccines (see pertinent ACIP recommendations).
- "The obvious convenience of giving already selected antigens in combined form should encourage consideration of using these products when appropriate."

[†] For complete text of both recommendations see your MSD representative or write to Professional Service Dept., Merck Sharp & Dohme, West Point, Pa. 19486.

M-M-R*

(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE | MSD)

Single-dose vials

M-M-R, given in a single injection, fits easily into your routine immunization program for well babies.

Given at age 12 months, M-M-R provides for vaccination early in life against measles, mumps, and rubella.

MSD suggested immunization schedule for well babies

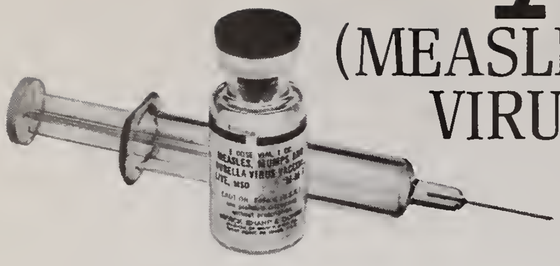
Age	**Vaccine(s)**
2 months	DPT (diphtheria-pertussis-tetanus) Oral poliomyelitis vaccine (triple)
3 months	DPT[1]
4 months	DPT Oral poliomyelitis vaccine (triple)
6 months	Oral poliomyelitis vaccine (triple)
12 MONTHS	**M-M-R (MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE, MSD)**

[1] This vaccination may be given at 3 months, 5 months, or at 6 months, depending on your preference or on the condition of the child.

Since vaccination with a live virus vaccine may depress the results of a tuberculin test for four weeks or longer, the test and the vaccine should not be given during the same office visit.

*Trademark of Merck & Co., Inc.

For a brief summary of prescribing information, please see following page.



M-M-R
(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE | MSD)

Single-dose vials

No untoward reactions peculiar to the combination vaccine (M-M-R) have been reported.

Moderate fever (101–102.9 F) occurs occasionally. High fever (over 103 F) occurs less commonly. On rare occasions, children who develop fever may exhibit febrile convulsions. Rash (usually minimal and without generalized distribution) may occur infrequently.

Since clinical experience with measles, mumps, and rubella virus vaccines given individually indicates that very rarely encephalitis and other nervous system reactions have occurred, such reactions may also occur with M-M-R. A cause and effect relationship, however, has not been established.

Excretion of the live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered the rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Must not be given to women who are pregnant or who might become pregnant within three months following vaccination.

Contraindications: Pregnancy or possibility of pregnancy within three months following vaccination; infants less than one year old; sensitivity to chicken or duck, chicken or duck eggs or feathers, or neomycin; any febrile respiratory illness or other active febrile infection; active untreated tuberculosis; therapy with ACTH, corticosteroids, irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; gamma globulin deficiency, i.e., agammaglobulinemia, hypogammaglobulinemia, and dysgammaglobulinemia.

Precautions: Administer subcutaneously; do not give intravenously. Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines; vaccination should be deferred for at least six weeks following blood transfusions or administration of more than 0.02 cc immune serum globulin (human) per pound of body weight, or human plasma.

Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur after vaccination.

Excretion of the live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered the rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Attenuated live virus measles and mumps vaccines, given separately, may temporarily depress tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be scheduled before vaccination, to avoid the possibility of a false negative response.

Before reconstitution, refrigerate vaccine at 2–8 C (35.6–46.4 F) and *protect from light*. Use only diluent supplied to reconstitute vaccine. If not used immediately, return reconstituted vaccine to refrigerator at 2–8 C (35.6–46.4 F), and discard after eight hours.

Adverse Reactions: Fever, rash; mild local reactions such as erythema, induration, tenderness, regional lymphadenopathy; parotitis; thrombocytopenia and purpura; allergic reactions such as urticaria; arthritis, arthralgia, and polyneuritis.

Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions.

Encephalitis and other nervous system reactions that have occurred very rarely with the individual vaccines may also occur with the combined vaccine.

Transient arthritis, arthralgia, and polyneuritis are features of natural rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Such reactions have been reported with live attenuated rubella virus vaccines. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after immunization should be considered as possibly vaccine related. Symptoms have generally been mild and of no more than three days' duration. The incidence in prepubertal children would appear to be less than 1% for reactions that would interfere with normal activity or necessitate medical attention.

How Supplied: Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the NIH Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin, with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8″ needle. Also in boxes of 10 single-dose vials nested in a pop-out tray with a separate box of 10 diluent-containing syringes.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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David O. Smith, M.D.
1881–1973

Dr. David O. Smith, a medical consultant in the Veterans Administration for many years, died June 2, 1973. He resided at 3761 Chesapeake Street, N.W., Washington, D.C.

Born in Derby, Iowa, he attended Simpson College in Indianola, Ia., and was a graduate of the University of Michigan, where he received his medical degree. He also studied at Oxford University in England.

Following medical school, Dr. Smith practiced medicine in Bismarck, North Dakota. In 1912, he was appointed to the surgical staff of the U.S. Hospital in the Panama Canal Zone, where he remained for three years.

Dr. Smith then joined the U.S. Public Health Service in Washington. In the early 1920's, he joined the Veterans Administration Staff and visited VA hospitals throughout the country before retiring some years ago.

He was a 57-year member of the Medical Society of the District of Columbia with Special status.

Dr. Smith is survived by his wife Grace, of the home address, and a sister, Dr. Alida Smith, of Washington.

Anna Catharine Q. Knop
1909–1973

Dr. Anna Catharine Q. Knop, a pediatrician and founding partner of the Yater Clinic in Washington, D.C. died July 20, 1973. She resided at 5912 Gloster Road.

Born in Buelkau, Germany, she attended Frankfort-on-Main, Bonn, Breslau, Duesseldorf and Freiburg Universities and received her medical degree from the University of Hamburg in Germany.

She served internships at University Hospital, Eppendorf (Hamburg), Augusta Victoria Hospital (Berlin) and Providence Hospital, Washington, D.C.

Her post graduate medical education was obtained at West London Hospital, Hammersith, London, England, and in bacteriology and pathology at Providence Hospital, Washington, D.C. She was a Fellow in Pediatrics of the Mayo Foundation, Rochester, Minnesota and received her Master of Science in Pediatrics from the University of Minnesota.

In addition to her work at the Yater Clinic, Dr. Knop was on the faculty of Georgetown University Medical School for more than 20 years, serving as a clinical full professor. She traveled extensively in connection with research and volunteer work for Care-Medico and other organizations and helped set up clinics in Algeria, the Bahamas and Guatemala. She authored and co-authored 12 published articles on medical subjects.

Dr. Knop was a Special member of the Medical Society of the District of Columbia and a member of the American Medical Association. In addition, she served as president of the District of Columbia Women's Medical Society in 1969. In 1970, she received the Pediatrician of the Year Award from Georgetown University Medical School.

She is survived by a son, Peter John Knop, and a grandchild, of Washington; and a sister, brother and two half-sisters, all of Germany.

Daniel B. Washington, M.D.
1904–1973

Dr. Daniel B. Washington, who practiced general medicine in the Washington area for 39 years and was a direct descendant of Colonel William A. Washington, kinsman to George Washington, died July 2, 1973.

Born in Washington, D.C., he received both his undergraduate and medical degrees from George Washington University. He served his internship at Sibley Hospital and was on the courtesy staff of all D.C. hospitals.

Dr. Washington was a Life member of the Medical Society of the District of Columbia, with a membership dating from February 1932, as well as a member of the American Medical Association.

He is survived by his wife, Mary Virginia of the home address; a daughter, Mrs. Walter C. Holmes of Silver Spring; four stepchildren, John Friedman of Brockeville, Betty Smith of Silver Spring, Judy Smith of Oxon Hill, and Carl Ressa of Gaithersburg; a sister, Mrs. John Morrison Kerr of Washington; and two grandchildren.

ECG Diagnosis

(from page 459)

INTERPRETATION:

1. (ECG #1) ST changes consistent with myocardial ischemia.
2. (ECG #2) Probable acute posterior myocardial infarction.

In the first tracing, the only significant abnormality is depression of the ST segments in leads V_2 through V_4 with slight depression in V_5. In ECG #2, the R wave has increased in amplitude and duration in leads V_1 through V_3. The ST-T contours in leads V_1 through V_4 represent mirror images of those which are characteristically found overlying an area of myocardial infarction. Instead of developing Q waves with elevated ST segments and inverted T waves, the mirror image shows abnormally large R waves, depressed ST segments and upright T waves. If these leads are viewed in a mirror, the similarity is obvious. These are characteristic changes of infarction of the posterobasal portion of the left ventricle—so called "true posterior" myocardial infarction. The remainder of the patient's hospital course was typical for a patient with acute myocardial infarction.

Edited by Robert R. Montgomery, M.D.

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The by-line, the author's given name and initial or given name alone should be supplied. The M.D. degree or highest academic degree should be listed for each author. Not more than six names should be included as authors, unless the communication is the report of a committee.

The footnotes, hospital and university affiliation when study was done, should be listed. Present affiliation and location (if different from that at time of study) should be given. Acknowledgements should be limited to persons, foundations, agencies or companies supplying drugs, funds or apparatus free of charge or otherwise making an extensive contribution to the study.

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McNeil Laboratories, Inc. 450
Merck, Sharp & Dohme Division of Merck & Company T-468–470
Pharmaceuticals Manufacturers Association T-441–443
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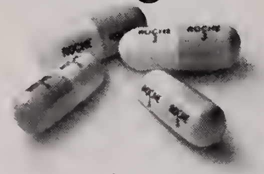

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President's Message 1
PSRO—Bane or Boon? Irving Burka, M.D.

AMA Council Statement on Venereal Diseases 3

SCIENTIFIC ARTICLES

Doctors, Digits and Disks. Charles S. Tidball, Ph.D., M.D. 473

Viral Hepatitis: Metabolic Studies During Acute and Convalescent Phase. Cdr. W. V. R. Vieweg, MC, USN, R. L. Piscatelli, M.D., J. T. Boone, M.D., R. E. Reitz, M.D., R. B. Berstein, M.D. and R. L. Weinstein, M.D. 480

Review of the Medical Management of Acute Variceal Bleeding from the Esophagus. James Apesos, B.A. 486

The Relationship of Hepatitis Associated Antigen (Australia Antigen) and Chronic Active Hepatitis—Review of Current Literature. Steven F. Mazer 490

The Postmastectomy Lymphedematous Arm. Guy F. Robbins, M.D., and William M. Markel, M.D. Forward by Margaret Kenrick, M.D. 495

SPECIAL ARTICLE

Community Health Aspects of Water Pollution Problems. Bailus Walker and Theodore J. Gordon 498

ECG Problems 497

The View Box 519

Howard E. Ticktin Fund 522

Committee Report 523
Colon-Rectal Cancer
Cancer Quiz

(continued)

Book Reviews 529
Principles of Clinical Electrocardiography. (Goldman) Reviewed by Gerald I. Shugoll, M.D.

Review of Physiological Chemistry. (Harper) Reviewed by Felix Friedberg, Ph.D.

Cardiac Hypertrophy. (Alpert) Reviewed by Benjamin Manchester, M.D.

Tissue Typing Techniques. (Dick and Barry) Reviewed by Phillip Periman, M.D.

Obituaries 535
Jerome H. Epstein, M.D.
Ella M. A. Enlows, M.D.

Information for Authors T-536

Advertising and Subscription Information T-537

Index to Advertisers T-537

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PRESIDENT'S MESSAGE

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PSRO—Bane or Boon?

IRVING BURKA, M.D.

Much has been written and said about the new law which establishes, for the first time, a professional service review organization applicable to medicare and medicaid patients while in the hospital.

No objective person can argue against the fact that this new legislation is a departure for American Medicine—from a method of practice which has been a part of our country's medical profession for many years. All of us, particularly those in private practice, have been trained and conditioned to a fundamental philosophy of non-interference in the doctor-patient relationship. This is particularly true where Government involvement is concerned. Nor can anyone argue that this legislation may be a first step in the evolutionary process of creating socialized medicine.

It is not difficult to understand and empathize with our colleagues who are both fearful and resentful of this government interference in our well-established norm of practice. We agree that it is increasingly difficult to practice medicine in a modern day environment where the physician must meet the requirements of both a professional and a small business man. Certainly more bureaucratic interference could become an additional burden to an already overburdened practitioner. I hope to convey to those who honestly oppose the entire concept of PSRO, that we, here on the local level, do understand.

The fact remains that this is now the law of the land. As responsible citizens engaged in an ethical profession, we must conform and obey the law. We have a great opportunity to demonstrate to the entire country that we, as responsible physicians, can use this instrument of law to improve the quality of health care and to implement and further stress continuing education. I sincerely hope that the question of cost control, which must be considered, shall come as the result of the above, rather than a primary purpose.

Using this same instrument and the corporate entity needed for its function, we could soon be in a position to negotiate with private carriers for fee reveiw and utilization by our own peers, which could result in greater benefit to our patients. This could completely eliminate the denial of payment by the carrier for services rendered and hospital costs—long after the patients' discharge from the hospital. We cannot deny that this is becoming commonplace and extremely difficult to cope with.

Remember, the law specifically puts the reviewing mechanism in the hands of licensed, practicing physicians and osteopaths who are active members of hospital staffs, and not in the hands of some bureaucratic government committee. We should do everything in our power to make it work, but, more than that, we must never permit the reviewing process to be conducted by any but our peers. This is where our vigilence must be directed and, in this, we must be united.

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American Medical Association

STATEMENT ON VENEREAL DISEASES

Gonorrhea ranks first (excluding influenza) and syphilis third among the reportable diseases in the United States. During 1972, there were 767,215 gonorrhea cases reported, 14.5% higher nationally than the previous year and more than double the number reported in 1965. Increases have occurred in all parts of the nation and in all age and sex groups, but the largest concentration of cases is in the 15-24 year age group. Allowance for both under reporting and failure to diagnose all cases as they occur suggests that the actual occurrence of gonorrhea infection last year was about 2.5 million.

The Center for Disease Control estimates that the reservoir of gonorrhea includes six to 800,000 females and about 100,000 males that are asymptomatic. To help reduce this reservoir of silent carriers, most states have implemented gonorrhea screening programs for females. The Center for Disease Control reports that from July 1972 to March 1973 there were 3,117,022 females screened and 158,604 (5.1%) had a positive test for gonorrhea. Of 664,110 females tested in private physician offices throughout the nation, 2.5% had a positive culture for gonorrhea. The Council urges medical societies to promote gonorrhea culture screening among females.

During 1972, syphilis morbidity (all stages) exceeded 91,000 reported cases. The number of congenital syphilitics under one year of age numbered 383 in 1972. Reported cases of primary and secondary syphilis (the infectious stages) numbered 24,429, up 3% from the previous year, with an estimated 85,000 cases occurring annually. Because large numbers have escaped detection over the years, it is estimated that if every person in the United States could be tested for syphilis today, about ½ million previously untreated cases would be found.

An important procedure used to identify persons infected with syphilis or gonorrhea is laboratory reporting to public health authorities of those persons who have a positive test for either. The patient is contacted through his own physician for diagnosis and treatment if necessary. The following states do not have laws or health department regulations that require laboratories to report persons with positive VD tests to health authorities: Alaska, Idaho, Indiana, Louisiana, Maine, Massachusetts, North Dakota, South Dakota and Washington. Experience has shown that many laboratories refuse to report persons with a positive test for venereal disease to the health department until it is required by law or regulation. The Council recommends that medical societies in these states take appropriate action for the enactment of laws or regulations that require laboratories to report the positive venereal tests.

With the exception of Wisconsin, all the states now have laws or regulations permitting the treatment of minors for venereal disease without parental consent. It is believed, however, that some of the states' laws and regulations are so worded to make them inadequate. Also, some of the states might improve their laws by broadening the age group definition of minors.

Physicians in private practice treat approximately 80% of the syphilis and gonorrhea that comes to diagnosis but report to public health departments only one out of every eight cases of syphilis and one out of every nine cases of gonorrhea they treat. Physicians should assist public health departments by reporting the venereal disease cases they treat. Medical societies are urged to cooperate and give broad support to public health authorities. Much effort must still be made by health departments and medical societies to foster mutual trust so that public and private medicine can work effectively for the control of both syphilis and gonorrhea. Most state and some local health departments have venereal disease interviewer-investigators who can work confidentially with the patient and his contacts to determine the source and spread of his infection. The Council urges the physician to utilize the services of these trained investigators.

Adequate therapy of venereal disease, using the right forms and dosages of antibiotics, is essential. Neisseria gonococci has shown the ability to develop resistance to penicillin to the point where the recommended dosage now is 4.8 million units of Aqueous procaine penicillin for the treatment of gonorrhea in both males and females. It is anticipated that additional changes in treatment may have to be made from time to time as increasing resistance becomes a problem or more effective antibiotics are discovered. For this reason the Council urges that medical societies impress upon their members the need for keeping abreast of changes in the recommended therapy of the venereal diseases.

The Council encourages the publication of more articles in professional journals on venereal disease and its control for the guidance of the profession. Medical societies are asked to support education of parents and the public through more extensive and imaginative use of all available media and through school curriculum.

The Council urges medical societies to acquaint their membership with the growing and alarming dimensions of the venereal disease problem. Physicians should take all appropriate measures to reverse the rise in venereal disease and bring it under control.

acute arthritic inflammation...heat that freezes

In acute rheumatoid arthritis consider Tandearil. The anti-inflammatory action of Tandearil quickly helps reduce heat, pain, swelling, and stiffness. Results are usually seen in 3 or 4 days. Try it for a week when the symptoms defy aspirin control.

Remember that Tandearil is not a simple analgesic. It should not be used on patients responding to routine therapy. Before using, please read the prescribing information. It's summarized below.

Tandearil® helps take the heat off

oxyphenbutazone NF

Geigy

Tablets of 100 mg.
Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Acute gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existence of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
(B)98-146-800-F (10/71)
For complete details, including dosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
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TA 9041

More than sleep.

your choice of sleep medication is wisely based on more than sleep-inducing potential

sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dal (flurazepam HCl); no depression of cardiac or respiratory func was noted in patients administered recommended or higher d for as long as 90 consecutive nights.

In most instances when adverse reactions were reported, they were mild, infrequent and seldo quired discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. ness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

sleep for 7 to 8 hou without need to repeat dosage

No sleep m cation has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia pati given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer n time awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to re dosage during the night.

eep with onsistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration, with no need to increase dosage.

Dalmane (flurazepam HCl) is a distinctive sleep medication—a
odiazepine specifically indicated for insomnia. It is not a bar-
ate or methaqualone, nor is it related chemically to any other
able hypnotic.
When your evaluation of insomnia indicates the need for a sleep
cation, consider Dalmane—a single entity nonnarcotic, non-
iturate agent proved effective and relatively safe for relief of
nnia.

DALMANE®

(flurazepam HCl)

When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE

ROCHE LABORATORIES
Div., Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Opinion & Dialogue

"Prescription drugs – who should determine the maker?"

Dispenser of Medicine

Clifton J. Latiolais
President
American Pharmaceutical Association

"Too many doctors are indiffe ent to the economic consequences their decisions." So stated a recent issue of *Medical News Report* (December 4, 1972), an independent weekly newsletter published by form AMA Chief Executive F. J. L. Blasingame, M.D.

Doctor, are you indifferent . . . ?

In discussing an anticipated in crease in Blue Shield rates, Dr. Blas ingame's newsletter had this to say:

"In general, it can be said, MD have given the impression they are not particularly concerned with the increase in cost of health care to the patients . . .

"True, an MD's training is primarily scientific, but in the real wor of practice, all of his scientific decisions have a price tag, or an econom impact. The economics of health ca beckon the practitioner's attention. Concern for economics of medicine

Maker of Medicine

C. Joseph Stetler
President
Pharmaceutical Manufacturers Association

When the pharmacist recommends that a drug product other th the one ordered be dispensed, the prescriber invariably permits the change when he feels the best interests of the patient will be served.

Shortcomings of Pro-Substitution Argument

The fact remains that it is nece sary for the prescriber to know that the change is being contemplated, and to be in a position to consent or demur. Without that opportunity, th unilateral decision of the pharmacis made in the absence of clinical know edge of the patient, could expose hi to needless risks, and in addition, jeopardize the relationship between the professions of Pharmacy and Medicine. In my view, there is nothi in the pro-substitution argument th offsets these risks.

The Issue of Drug Knowledge

Substitution advocates claim that the primary justification for changing the rules is the desire to better utilize pharmacists' knowled about drugs. Yet the pharmacist's task to keep current on the entire field of drug therapy, to some degre puts him at a disadvantage. Most often, a practicing physician will nee expert knowledge of no more than 2

Advertisement

uld be an obligation of medical ctice...

"Medical societies ought to con- t continuing campaigns to point the substantial savings that could realized thru deductible insurance protection for catastrophic ill- s. At the very least, they should, in patients' interest, question the tics of any insurance organization t raises health care costs by forc- policyholders to buy insurance y may not need or want and prob- y won't ever use.

"Too many doctors are indiffer- to the economic consequences of ir decisions. Too many, for ex- iple, habitually hospitalize patients the convenience of the MD. It's nsense to deny such habits exist...

"Doctors, thru their medical so- ties, have unhesitatingly appealed their patients for support in the ht against government interference h the private practice of medicine. d the public in the past has re- onded. It's time the American Med- l Association and state and local edical societies paid off the debt by cisive action to hold down the cost medical care."

st of Drugs

Insurance rates and hospital arges are only two factors in health care costs. The cost of drugs—both prescription and nonprescription—is another.

And when it comes to drug costs, the nation's pharmacists *are concerned.* Through their national professional society, the American Pharmaceutical Association, pharmacists are advising the public to use nonprescription medication cautiously and conservatively, and to seek the advice of their pharmacist before selecting or purchasing such drugs.

Outdated Laws

The pharmacist also is aware that when it comes to prescription drugs, often he has an even greater opportunity to reduce the cost to the patient—with no sacrifice in the quality of the medication dispensed. But in many states, outdated and antiquated laws prevent the pharmacist from engaging in drug product selection. "Drug product selection" simply means that the pharmacist functions in the patient's interest by consciously choosing, from the multiple brands available, a low-cost quality brand of the specific drug to be dispensed in response to the physician's prescription order.

Much *misinformation* has been purposely spread by those who stand to gain financially by maintaining high drug costs to the public. An endless stream of propaganda has emanated from the drug industry in an effort to persuade the medical profession that these so-called anti-substitution laws should be retained. And as long as these laws are retained, the drug industry will continue its current marketing practices which contribute unnecessarily to high drug costs to patients. These practices also are inviting government agencies to expand their restrictive controls on physicians and pharmacists.

APhA Efforts

As pharmacists, we are concerned about health care costs. We hope that every physician shares our concern on this vital issue, and will give his personal support to the constructive efforts APhA has undertaken in the interest of all patients.

(For a complete discussion of drug product selection, you are invited to request a free copy of the "White Paper on the Pharmacist's Role in Product Selection" from: American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, D.C. 20037.)

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30 drugs that he selects to treat the ajority of conditions encountered in s practice. Moreover, the physi- an's choice of a specific brand is ased on his knowledge of the pa- ent's medical history and current ndition, and his experiences with e particular manufacturer's oduct.

Some substitution proponents ave argued that the dispensing of a escription is a simple two-party ansaction between the pharmacist d the patient, and that a substitut- g pharmacist may avoid even a chnical breach of contract by simply otifying the patient that he is making e substitution. I would judge that w courts would be sympathetic ward a pharmacist who substituted ithout physician approval and who ndertook a legal defense that seeks make the patient responsible for e pharmacist's actions.

educed Prescription Prices?

Substitution advocates are ggesting to the consumer, and par- cularly the consumer activist, that educed prescription prices could llow legalization of substitution. e have seen absolutely no evidence justify this claim. To the contrary, xperience in Alberta, Canada, where ubstitution is authorized, suggests the opposite.

Many pharmacists understandably are concerned about the cost of maintaining multiple stocks of similar products. While there is no doubt that inventory costs rise when additional brands are stocked, it would be interesting to know how much they rise, and how many pharmacists actually stock *all* brands—of, say, ampicillin or tetracycline—or how long they keep "slow moving" products on their shelves before they are returned for credit. To ask that the industry eliminate multiple sources is to ask competitors to stop competing.

Drug Substitution—A License for the Unethical

Anti-substitution repeal would favor "corner cutting" pharmacists and manufacturers. For them, free substitution would be not a right, but a license. As an aftermath, it is quite likely that the confidence of both physicians and patients in the profession of Pharmacy would be eroded, as revelations about the unconscionable behavior of an undisciplined few were magnified in the press or in professional circles.

Summary

In short, what the American Pharmaceutical Association advocates as a broad-spectrum panacea looks to us to be not only a minority view (advocacy of substitution is by no means a uniform policy in Pharmacy), but also an extraordinarily costly and ineffective remedy, whose side effects are odious. We believe (1) that an impressive majority of pharmacists prefer to work with Medicine and with industry, for the consumer, and for the general good, (2) that they seek the privilege to substitute when the patient might gain and when the patient's doctor agrees, and (3) that they seek to work for the resolution of genuine grievances openly and professionally.

(For amplification of PMA views, please write for our booklet, "The Medications Physicians Prescribe: Who Shall Determine the Source?" It is available from: Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C. 20005.)

Pharmaceutical
Manufacturers Association
1155 Fifteenth Street, N.W.
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P·M·A

ROCHE announces
new

BACTRIM^{T.M.}

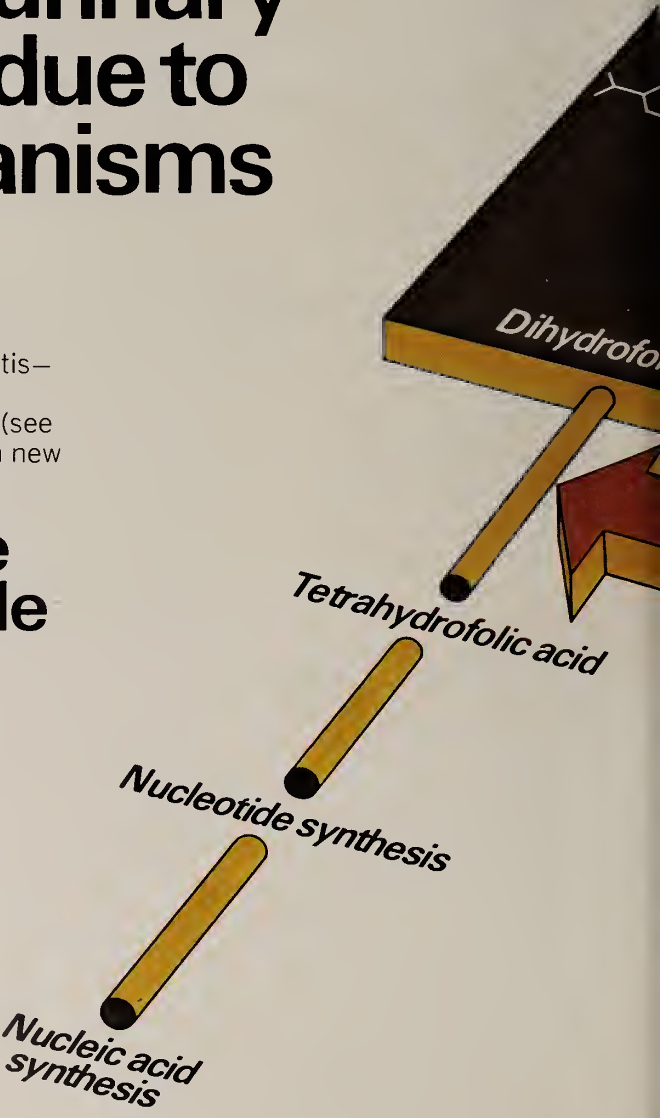
Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

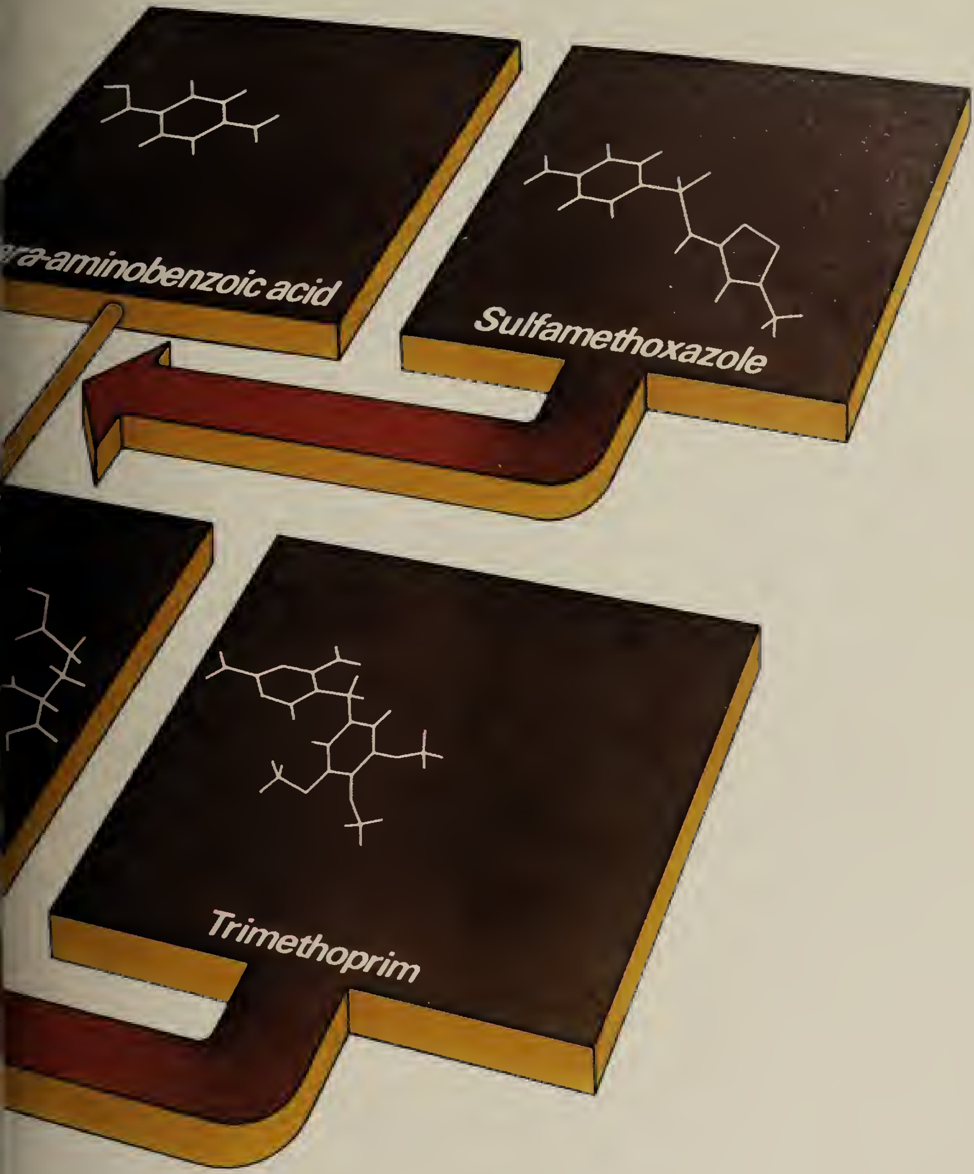
a new type of antibacterial for a two-pronged attack against chronic urinary tract infections due to susceptible organisms

Bactrim is highly effective in the treatment of these infections—primarily pyelonephritis, pyelitis and cystitis—when due to susceptible organisms. This efficacy is related to the unique mode of action against bacteria (see illustration), an action that, in effect, makes Bactrim a new type of antibacterial.

Bactrim interrupts the life cycle of susceptible bacteria

Unique mode of action interrupts the life cycle at two important points, thereby impeding the production of nucleic acids and proteins essential to these bacteria. These consecutive interruptions occur because sulfamethoxazole and trimethoprim resemble naturally existing substrates. By competitive replacement of these substrates, they inhibit further synthesis.




ara-aminobenzoic acid
Sulfamethoxazole
Trimethoprim

ROCHE

new BACTRIM™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

Before prescribing, please see complete product information on last page of advertisement.

Excellent clinical response in chronic urinary tract infections even with obstructive complications

A multiclinic, double-blind study* of response to a ten-day course of therapy in 471† patients with chronic urinary tract infections demonstrated the superiority of Bactrim. On the 10th day after initiation of therapy, 91.7% (of 168 patients) showed significant bacteriological response to Bactrim, compared with 81.2% (of 144 patients) to trimethoprim and 64.5% (of 155 patients) to sulfamethoxazole. More than half of these patients had obstructive complications.

Excellent response maintained

Bactrim proved equally impressive in maintaining this bacteriological response. In the above study, after a ten-day course of therapy with Bactrim, 68.4% of patients with chronic urinary tract infections *maintained* response for up to 42 consecutive days, compared with 59.7% with trimethoprim and 44.4% with sulfamethoxazole. These results are particularly noteworthy considering the number of patients with obstructive complications—cases regarded as being notoriously difficult to treat.

Prescribing considerations

Clinical Limitations: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections. Not recommended for children under twelve.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period.

Warnings and Precautions: Both sulfamethoxazole and trimethoprim have been reported to interfere with hematopoiesis. Complete blood counts should be done frequently. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued. Bactrim should be given with caution to patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. Maintain adequate fluid intake. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Adverse Effects: Among the most common side effects are nausea, vomiting, rash, leukopenia and elevations in SGOT and creatinine.

Usual adult dosage: two tablets every twelve hours for 10 to 14 days; no loading dose required.

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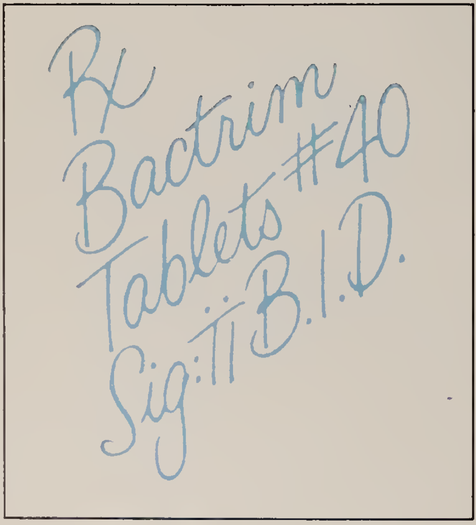
*Data on file, Hoffmann-La Roche Inc., Nutley, N.J. 07110

† 4 patients not available for evaluation at day 10.



Rx
Bactrim
Tablets #40
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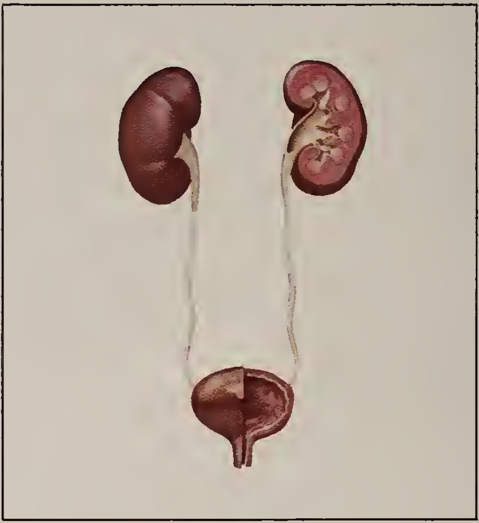

new **BACTRIM**™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N J 07110

Complete Product Information:

Description: Bactrim is a synthetic antibacterial combination product, available in scored light-green tablets, each containing 80 mg rimethoprim and 400 mg sulfamethoxazole.

rimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. t is a white to light-yellow, odorless, bitter compound with a molecular weight of 290.3.

Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl) sulfanilamide. It is n almost white in color, odorless, tasteless compound with a molecular weight of 253.28.

Actions: *Microbiology:* Sulfamethoxazole inhibits bacterial synthesis f dihydrofolic acid by competing with *para*-aminobenzoic acid. rimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

n vitro studies have shown that bacterial resistance develops more slowly with Bactrim than with trimethoprim or sulfamethoxazole alone.

n vitro serial dilution tests have shown that the spectrum of antibacterial activity of Bactrim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis* and indole-positive proteus species.

Representative Minimum Inhibitory Concentration Values for Bactrim-Susceptible Organisms
(MIC—mcg/ml)

Bacteria	Trimethoprim alone	Sulfamethoxazole alone	TMP/SMX (1:20)	
			TMP	SMX
Escherichia coli	0.05—1.5	1.0 —245	0.05—0.5	0.95— 9.5
Proteus spp. indole positive	0.5 —5.0	7.35 —300	0.05—1.5	0.95—28.5
Proteus mirabilis	0.5 —1.5	7.35 — 30	0.05—0.15	0.95— 2.85
Klebsiella-Enterobacter	0.15—5.0	0.735—245	0.05—1.5	0.95—28.5

Human Pharmacology: Bactrim is rapidly absorbed following oral administration. The blood levels of trimethoprim and sulfamethoxazole are similar to those achieved when each component is given alone. Peak blood levels for the individual components occur one to four hours after oral administration. The half-lives of sulfamethoxazole and trimethoprim, 10 and 16 hours respectively, are relatively the same regardless of whether these compounds are administered as individual components or as Bactrim. Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. Free sulfamethoxazole and trimethoprim blood levels are proportionately dose-dependent. On repeated administration, the steady-state ratio of trimethoprim to sulfamethoxazole levels in the blood is about 1:20.

Sulfamethoxazole exists in the blood as free, conjugated and protein-bound forms; trimethoprim is present as free, protein-bound and metabolized forms. The free forms are considered to be the therapeutically active forms. Approximately 44 percent of trimethoprim and 70 percent of sulfamethoxazole are protein-bound in the blood. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim to an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Excretion of Bactrim is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. When administered together as in Bactrim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis*, and, less frequently, indole-positive proteus species).

***Important note:* Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections.**

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see Reproduction Studies).

Warnings: Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Bactrim. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued.

At the present time, there is insufficient clinical information on the use of Bactrim in infants and children under 12 years of age to recommend its use.

Precautions: Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Adverse Reactions: For completeness, all major reactions to sulfonamides and to trimethoprim are included below, even though they may not have been reported with Bactrim.

Blood dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

Dosage and Administration: Not recommended for use in children under 12 years of age.

The usual adult dosage is two tablets every 12 hours for 10 to 14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

How Supplied: Tablets, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 1000; Prescription Paks of 40, available singly and in trays of 10. Imprint on tablets: ROCHE 50.

Reproduction Studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. However, in one study, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

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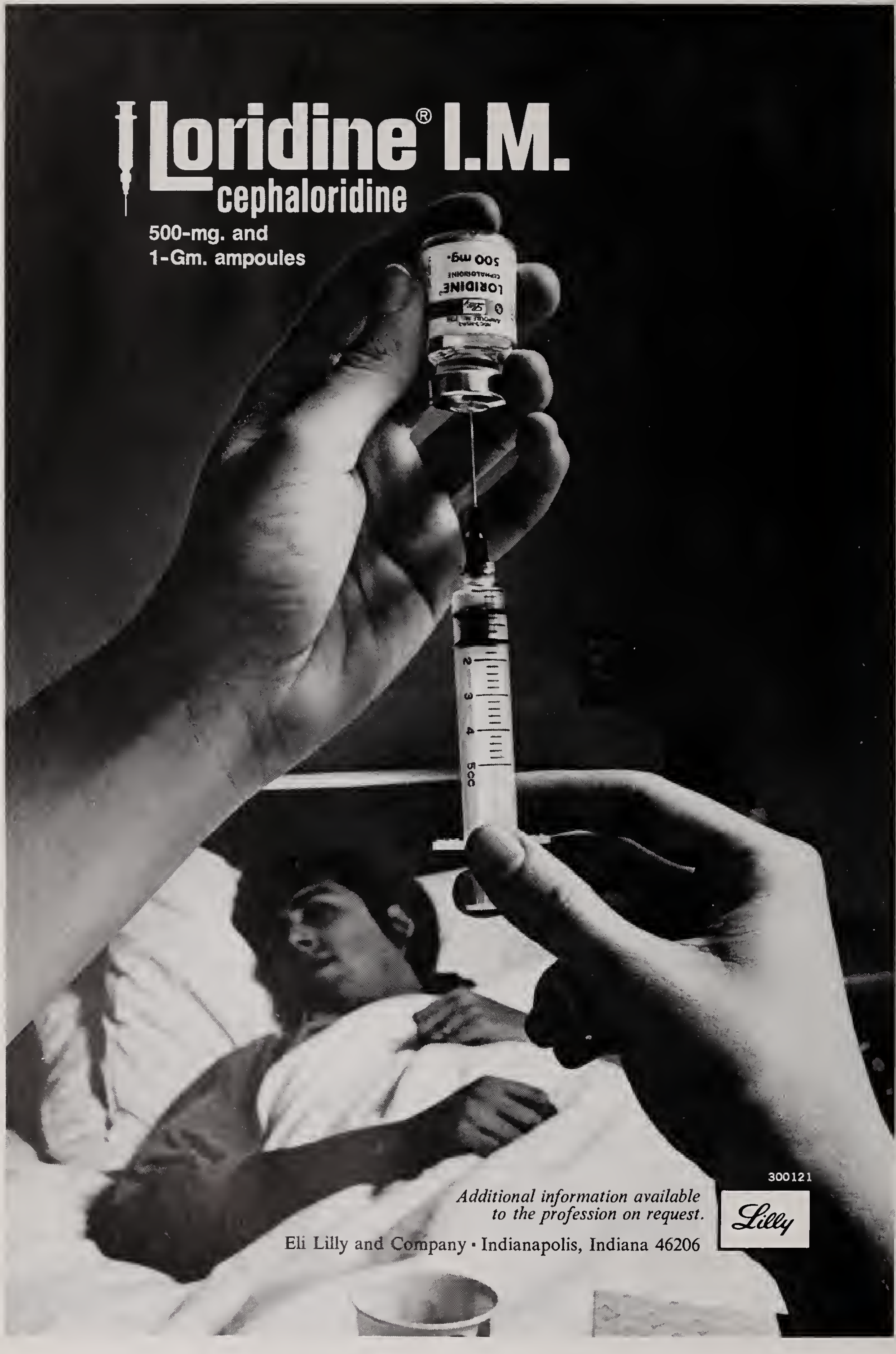

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Doctors, Digits and Disks

CHARLES S. TIDBALL, PH.D., M.D.*

Introduction

Lest any should be confused by the title, this communication is *not* directed only at hand surgeons or orthopods. It deals with the implications of computer technology on medicine and is commended to every physician, regardless of the nature of his or her practice. Man tends to be threatened by that which he does not understand. Nowhere is this more clearly evident than in the reaction of many physicians to the impending computer technology which promises to change the practice of medicine much as it has already altered our concepts of which is possible and impossible in such disparate fields as motel reservations, manned-space flight, and medical information retrieval.

Let us illustrate the scope of the problem by discussing a commonly held misconception: namely, that computers are impersonal and dehumanizing. This assertion is paradoxic because one of the advantages of computer technology is the ability to render a specific service to an individual at a high level of precision and with considerable speed. The belief comes about because many of our transactions with machines are based on numbers rather than names, which evolved because computers were originally designed to function with numbers. When they are made to process letters, these have first to be changed to numbers for the benefit of the machine and then changed back into letters for the final application; to minimize the number and extent of such conversions, the people who first programmed computers substituted multi-digit numbers for names. Thus it is not computers which are impersonal and dehumanizing, but the people who program them and the administrators who determine how many refinements will be permitted in a particular program. Unfortunately, this adds only to the ageless evidence that man is still his own worst enemy.

A second important point is an appreciation of what computers can and cannot do in the field of medicine. A computer can be programmed to interview a patient; it can do so with greater thoroughness than some physicians, especially if the latter are distracted or in too big a hurry. A computer can be programmed to read and interpret an electrocardiogram; it can do so with greater uniformity than individual interpreters at a heart station, but it still has trouble identifying certain disturbances of rhythm. A computer can be programmed to store medical records in random access disk files where they can be interrogated so that information retrieval becomes efficient and accurate. But, computers cannot be programmed to substitute for informed medical judgment. We need not be threatened by these devices. They have been designed by mortal men to assist us in the important work we perform. They are only the latest in an armamentarium of technological adjuncts which improve the ability of the physician to accomplish his appointed tasks.

Before we can make full utilization of this new equipment, however, we must learn under what circumstances the often extensive financial investment associated with access to these devices has the best chances of being successful. To that end, this primer on computer fundamentals is offered.

The Speed of the Digital Computer

An adding machine or a rotary calculator performs arithmetic at speeds analogous to that of a human being. Thus persons who are unusually gifted may perform calculations mentally and keep up with these machines, if the numbers are not too large. By contrast, the speed of even the earliest digital computers exceeded human capacities. Since then we have gone through four generations of computer design. Electro-magnetic relays were replaced by vacuum tubes which gave way to transistors and were themselves superseded by integrated circuits. Each of these substitutions yielded improvements with regard to speed, so that today the duration of a single cycle of machine operation is measured in nanoseconds, the one billionth part of a second. It is difficult for the human mind to comprehend that a man-made machine can actually carry out many millions of steps within a single second.

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The Precision of the Digital Computer

Two factors make the computer very precise in its operation with numbers. It is capable of dealing with very large numbers without having to round them off to smaller numbers during the course of a calculation. The process of rounding off which is used in manual calculation is one of the principle sources of error in the final answer. Secondly, large computers have a checking quantity known as parity, which provides an internal safeguard against an incorrect transfer of a number from one portion of the system to another. If the parity check is not fulfilled, the computer automatically copies the number again until a proper parity tally is obtained. Thus the degree of error in a modern computer is generally less than one part in a million.

The Storage Capability of the Digital Computer

Unlike human memory, storage in the computer is positive and permanent. When this is coupled with a large potential size of storage, depending on the individual computer and its intended use, we arrive at one of the reasons why it is difficult for human beings to understand computer capabilities. Digital computers have several different levels of memory depending on how rapidly the information must be made available: the main memory, which is often called core memory because it is made up of ferro-magnetic beads or cores; disk memory, which consists of spinning platters with surfaces that can be specifically magnetized; and tape memory where the information is stored on magnetic tape that can be reeled from place to place automatically by the computer. The main memory is the fastest and also the most expensive. It has the disadvantage that the information cannot be removed from the computer without first transferring it to another form of memory. The disk memory, although several orders of magnitude slower than core memory, can store large amounts of information at reduced cost. In both core and disk memory the information is said to be randomly accessible because any individual item can be retrieved without first having to sort through a large number of other items. Tape memory is not randomly accessible and is very slow compared to disk memory, but it has the advantage of being a convenient way to store information outside the computer in a form which permits easy re-entry as desired.

Information Representation in the Digital Computer

The modern digital computer is inherently a simple counting device. In order to satisfy engineering requirements of speed, simplicity, and reliability, the counting is done with elements that are only capable of two states. Although various terms have been used to express these states depending on the frame of reference, ultimately the representations 0 and 1 are used to designate the state of the counting elements. Since only two states are possible, we say that numerical representation in the machine is binary. This is an important point to appreciate: the only language the machine can understand is a language whose entire alphabet is comprised of the two characters 0 and 1.

Just as in ordinary language we tend to group letters into words, so in computer language the zeroes and the ones are grouped into words with one important difference. For a given model of computer, every word is the same length as every other word. The number of characters in a computer word is often referred to as the number of bits. Thus to say that a computer has a 16 bit word, means that the zeroes and ones are grouped 16 at a time for processing by the machine. Occasionally, especially with computers that have a large number of bits per word, the term byte is used to designate a subdivision of the word: 32 bit words are often subdivided into bytes each of which contains 8 bits. The use of the concept byte is also related to storing letters in the computer since 8 bits are generally required to designate one ordinary letter.

Even when clusters of zeroes and ones are broken up into words or bytes, they are unintelligible to the average human being. Therefore numeric representations of sequences of zeroes and ones have been used to help practitioners of computer technology grasp what information or instruction is being stored in a particular register of the machine at any given time. Two popular such representations are the octal and the hexadecimal number systems. The former is based on grouping bits three at a time and is well suited to computers with 12, 18, or 36 bit word length; the latter, based on grouping bits by fours, is used for computers whose word lengths are multiples of four or eight. In Table 1 can be seen examples of these various number representations. Note that in the octal system there are no eights or nines; similarly in hexadecimal, the letters A through F are added to create a number system with 16 digits. Although these numeric representations seem awkward to those of us who are used to the decimal number system, they represent such an improvement over remembering sequences of zeroes and ones that

TABLE 1: Number Representations for Sequences of Zeroes and Ones

Decimal Number	Binary Number (3 groups of 3 bits)	Octal Number	Binary Number (2 groups of 4 bits)	Hexa-decimal Number
0	000 000 000	000	0000 0000	00
1	000 000 001	001	0000 0001	01
2	000 000 010	002	0000 0010	02
3	000 000 011	003	0000 0011	03
4	000 000 100	004	0000 0100	04
5	000 000 101	005	0000 0101	05
6	000 000 110	006	0000 0110	06
7	000 000 111	007	0000 0111	07
8	000 001 000	010	0000 1000	08
9	000 001 001	011	0000 1001	09
10	000 001 010	012	0000 1010	0A
11	000 001 011	013	0000 1011	0B
12	000 001 100	014	0000 1100	0C
.				
.				
.				
24	000 011 000	030	0001 1000	18
.				
.				
.				
31	000 011 111	037	0001 1111	1F
.				
.				
.				
42	000 101 010	052	0010 1010	2A
.				
.				
.				
84	001 010 100	124	0101 0100	54

computer programmers use them routinely for certain kinds of programming tasks.

Generalized Scheme of Computer Architecture

It will now be advantageous to describe, in an admittedly simplistic manner, the building blocks which are common to all digital computers. In Figure 1 these components are depicted in a diagram which indicates the relationships between them. All computer components are divided into two general categories: the central processing unit which is often called the "mainframe" or the "CPU", and all other devices which are called peripheral units or simply "peripherals". The CPU consists of three sections: a control unit, an arithmetic unit, and the computer's main memory.

We can gain an appreciation of how computers operate by indicating the necessary sequence of events to accomplish a simple task such as the addition of two and five.

1. First the instruction that addition is to be performed must be entered into the input device and transferred to the arithmetic unit.
2. The control unit must be advised that the sequence of zeroes and ones which now resides in the arithmetic unit should be interpreted as an instruction as opposed to primary data.
3. In preparation for addition the arithmetic unit would now be reset to zero.
4. The first number, namely two, would be entered in the input device and transferred to the arithmetic unit in the appropriate binary form.
5. The second number, five, would then be transferred from the input device. Since the arithmetic unit has not been reset to zero between steps 4 and 5, we now have in the arithmetic unit a sequence of

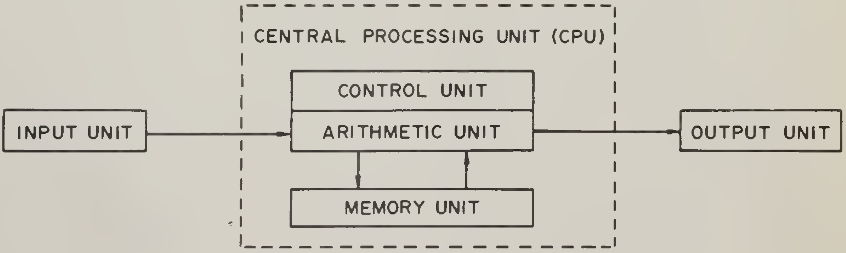

FIGURE I

Fig. 1. Building blocks in a digital computer installation.

zeroes and ones which represents the sum of the numbers we have entered.

6. In order for someone to know that this operation had in fact been carried out, it is necessary for the control unit to cause the value currently in the arithmetic unit to be transferred to the output unit preferably converted from binary representation back to the decimal number system.

In our simple example, the memory unit was not required. When more complicated procedures are to be carried out, the memory unit is used not only to store sequences of instructions called programs, but also to save any intermediate values required in the course of the calculations. It may be difficult to appreciate, but all computer programming ultimately must be reduced to simple incremental steps as illustrated in the example above.

Two Major Categories of Computer Utilization

As computers were developed, it was realized that these expensive devices required efficient utilization to justify their large initial cost. Two approaches to this problem emerged: first, which permits the computer to schedule individual tasks one after the other, is called "batch-processing"; second, which provides for a number of tasks to be accommodated by the computer apparently simultaneously, is called "time-sharing". Batch-processing is most suitable for such large tasks as payroll production, sending out bills, creating computerized files, or generating periodic reports. Time sharing, on the other hand, excels in those tasks which involve flexibility and minute to minute intervention by the human being undertaking the tasks; therefore it is used for inventory control, patient interviewing, citation retrieval, and computer assisted education. The largest computer facilities are able to undertake both batch-processing and time-sharing at the same time, but this is not true of all computer centers.

Levels of Interaction in Computer Systems

Just as the word hardware is used to refer to computer equipment, the term software is used to refer to the instructions to the equipment. This is somewhat of an oversimplification because there are at least three different levels of software with which to be concerned. As we try to understand how a computer functions we will take up each of these levels in turn.

Operating Systems—A digital computer, by itself, is a rather helpless device. It is entirely dependent on a set of instructions which permit it, or a human operator, to determine what task it is going to perform next. That portion of the total software is known as the "operating system" and varies widely in complexity and capability with the size of the computer and the number of features available on the machine. In its simplest form, the operating system enables a user to load a program into the main memory unit of the computer and then tells the computer at what location in memory to begin execution. More sophisticated operating systems permit several programs to be processed simultaneously, which is called multiprogramming, and to keep track of many separate tasks even when they are being accomplished at vastly different speeds.

Computer Languages—As indicated earlier, the only language that a digital computer understands is binary, or "machine language" as it is sometimes called. One might legitimately ask why the machines were designed in this peculiar way. The answer is that the simplest, fastest, and most reliable device to be used as a computer component is a two position switch which is either on (on = 1) or off (off = 0). Once again the convenience of the machine has been placed ahead of the convenience of man, but perhaps this is justifiable when one takes into consideration the strenuous requirements in terms of speed and reliability demanded of computer components.

The next step in intelligibility is what is known as "assembly language." Here the communication with the machine is done with a restricted set of abbreviations, called mnemonics, and symbols which are substituted for numerical representation of locations in the computer's memory. A program written in assembly language is called a "source program." Then the power of the computer is utilized to translate (the technical term is compile) the assembly language source program into a machine language version of that program. However, assembly language programming is really intended for computer professionals.

A third level of intelligibility is provided by languages such as FORTRAN, COBOL, BASIC, or FOCAL which are called high-level languages. The communication in these languages is even closer to natural Englishlanguage, especially where the applications have a mathematical context. Some high-level languages such as FOCAL and APL are known as interpreter languages—the binary is created at each step in the program. Others, such as FORTRAN or COBOL, require that the entire program be compiled into a single machine language version at one time. Thus any small variation in the program necessitates compiling a new set of binary instructions. An interesting feature of BASIC is that it has both an interpreter and a compiler; thus programs written in BASIC are stored in source but executed in binary. Thus editing a program in source is readily available; when the correction is completed the program is recompiled for execution in binary. Where storing a program in its binary version is available, less room is required to store it on magnetic tape or disk than the source version.

One of the advantages of these generalized languages is that they are relatively the same from computer to computer, whereas each individual machine has its own binary and even assembly language instruction sets. Unfortunately, this advantage is more true in theory than in observance. There are many different versions of popular high-level languages such as FORTRAN and BASIC and often these versions are not exactly compatible from machine to machine.

Application Programs—In this final level of our discussion of software, we are dealing with the ultimate set of instructions which permit the computer to accomplish a specific task or application. If the purpose is to create a file of patient names which will store their office visits and treatment record, and can then be used to create monthly statements, that task can be done on a variety of computer equipment, with a variety of operating systems and in a variety of programming languages. In spite of this multiplicity of approaches, the final application program, which is what an office assistant would actually be working with, might be identical.

Another way of saying this is that good application programming attempts to minimize the restrictions imposed by the equipment, the operating system, or the computer language. Of course the size of CPU, the amount of available memory, and the extent of bulk storage, have a great deal to do with the flexibility of the computer system. But with good design, the user of an interactive computer system need not be concerned with these matters. We say that the way in which the system accomplishes its work has been rendered transparent to the ultimate user. This, the theoretical goal of application programming, is never realized completely; however just as one need not understand how his automobile actually works to drive it, one can derive considerable utility from a computer terminal without having to understand how the system is accomplishing each specific task. The analogy is useful to make an additional point, one does have to learn how to drive an automobile. The knowledge required to do this is a small fraction of what must be known to repair it or to design a new one. So it is with interactive computing. A basic minimum of skill is needed to know how to make the connection to the computer system and how to interact with it successfully, but this is a small fraction of what one needs to appreciate if one desires actually to write application programs. Similarly, writing application programs in a high-level language is a relatively simple task. Therefore many users will learn enough about the language they use frequently to make the minor modifications in their application programs which individualizes them for their own particular requirements.

The ability to refine continually a program until it does exactly what one desires it to do is the great virtue of the computer, particularly when it is used interactively. Then because our requirements do change with time, ability to modify that program after it is considered perfect is also important. This is called software maintenance and is every bit as necessary as equipment, or hardware, maintenance. One should never purchase computer services without a clear understanding of who will be responsible for software maintenance and how it will be charged. Software that does not need to be altered exists only in the mind of the less-than-entirely-scrupulous, computer technology salesman.

Computer Versus Computer Terminal

The newcomer to computer technology sometimes is unclear of the distinction between computer and computer terminal. When computer meant a room full of large equipment, as is true for most batch-processing machines, and computer terminal meant the noisy teletype machine, the distinction was fairly obvious. Now with the advent of mini-computers and more complex terminals, the difference between a sophisticated terminal and a small computer is not so easy. In fact the term "intelligent terminal" has been coined to describe machines that have some stand-alone computing power but rely on a larger computer for assistance with bulk storage and the execution of larger programs. The important point to appreciate about terminals is that they generally rely on an ordinary telephone line for the connection to a computer. It is possible that most terminals will be acquired for communication with a single time-sharing computer, but this is not necessarily the case. A terminal is capable of communicating with a large variety of computers providing that the user has bona fide access to the remote computer.

At George Washington University Medical Center, our medical students communicate with the computers at Massachusetts General Hospital, Ohio State University, the University of Illinois at the Medical Center, The State University of New York at Albany and the National Library of Medicine with the same terminals that they use to connect to our own educational time-sharing computer. It is not even necessary to pay long-distance telephone charges for such use because of a Biomedical Communication Network maintained by the Lister Hill Center of the National Library of Medicine. Thus one should think of a computer terminal as a versatile device with potential access to the entire biomedical communication capability of the nation.

Reliability of Computational Devices

No discussion of computer fundamentals would be complete without bringing up the matter of reliability. If we are to substitute the computer terminal for an interacting human being, we have to have two types of assurance: first that the automated system will be at least as thorough as the human being, and second that the automated system will not become unavailable due to electronic failure just when we have become dependent on it. On the first point considerable data have already been accumulated. In the matter of acquiring patient information, an automated system is well accepted by a majority of patients and generally more thorough than the average physician. As to equipment failure, two approaches are possible. The manufacturer provides preferential maintenance service which guarantees repair effort on non-functioning equipment according to an established schedule. This is costly and does not prevent a failure at a crucial time, but it does assure that the equipment will be returned to complete functioning as soon as possible. The second approach is to design the computational facility with a certain amount of redundancy such that, if a key component fails, the processing load can be shifted to a duplicate. This capability is generally available in the larger commercial time-sharing services which have networks consisting of many separate computers to assure that customers will always have access to the service they require. Such reliability may necessitate storing key programs on more than one computer, but the extra storage charges are a small price to pay for the assurance that equipment failure will not prevent utilization of this new resource when it is most needed.

Relation of Computer Technology to Medical Practice

If the reader has perservered and made some sense out of the preceding sections, he is now in a position to understand some of the difficulties which attend the application of this new technology to the practice of medicine. Lest any should doubt, the author is enthusiastic about the application of high-speed computational equipment for a broad variety of tasks in biology, medicine, and education. Nevertheless, so that false expectations are not raised, it is important to state in clear terms what can be done today, what is likely to be available soon, and what appears to be an unlikely development in the near future.

Today some very exciting programs are available in a variety of areas of interest to the physician. These include patient simulations for teaching special skills, computerized clinical consultant services, bibliographic citation retrieval, and even practical examinations for certification in some of the specialty boards. However, the surface is barely scratched as to what should be available to provide even a superficial coverage over the entire breadth of medicine.

In the near future we can expect increasing computerization of hospital records, increasing automatization of office visits and billing procedures, and increasing transmission of charts, Xrays, and so on over telephone lines. But, before you hurry out and acquire a computer terminal, it would be wise to appreciate that today you will be in the vanguard of what is a nationwide research and development effort. If you enjoy doing it as a hobby, well and good; but it would seem unlikely, at the moment, that acquiring a computer terminal would save either much time or money. This is because there is not yet enough software directed at the physician's requirements.

Do not expect instant computer diagnosis for the entirety of medicine in the near future. Some people are working on this problem but it is very, very complex and involves a complete

TABLE 2: Partial List of Programs Available from the Biomedical Communication Network

- Massachusetts General Hospital
  - Abdominal Pain
  - Acute Joint Pain
  - Anticoagulant Simulator
  - Cardiac Arrythmias
  - Cardiac Simulation
  - Cardiopulmonary Resuscitation
  - Coma
  - Diabetic Ketoacidosis
  - Digoxin Dosage Advisor
  - Drugs in Renal Failure
  - Hypertensive Emergencies
  - Idiopathic RDS in the Newborn
  - Jaundice
- Ohio State University
  - Acid-base Balance
  - An Introduction to Computer Assisted Instruction
  - Anticoagulant Medication
  - Developmental Task Groups
  - Juvenile Diabetes
  - Medical Terminology
  - Ophthalmoscopic Interpretation
  - Psychotropic Medications
  - Review Topics for Medical Personnel
  - Septic Shock Care
  - Short Topics for Patient Usage
- University of Illinois at the Medical Center
  - Computer-Aided Simulation of the Clinical Encounter
  - Computerized Random Item Bank

reorganization of the way in which computers work. Man in a split-second is able to recognize patterns. The neurophysiological techniques he uses to do this are not yet understood, therefore it is not possible to incorporate them into computer technology. Until they are, the problem of computer diagnosis will remain an elusive goal.

How to Become Involved in Computer Technology

This is too broad a subject to cover in this short space but a few clues can be indicated. Most of the major medical center libraries have computer terminals. These were acquired to access a program called MEDLINE which is the National Library of Medicine's computerized citation retrieval service. At George Washington University Medical Center it is utilized daily by house officers who want up-to-date references on the patients they are treating. The major teaching hospitals have computer terminals and access to the Biomedical Communication Network referred to earlier. In Table 2 is a partial list of some of the program titles which can be retrieved.

Finally, you might consider adding a computer terminal to your office equipment but here a few words of warning are appropriate. More money will be spent on software development than hardware acquisition. Most computer systems take a year or more to become functional in a particular environment. Rely on a satisfied user for advice rather than a computer technology salesman; if the salesman cannot provide you with a satisfied user, be especially careful. Expect that your system will change with time; usually this means that you will increase your investment in hardware or software. The greatest value of computer systems is the relative ease with which they can be improved. But, if you don't enjoy such a dynamic state, it may be better to wait until computer technology in support of medical practice is further advanced.

Viral Hepatitis: Metabolic Studies During Acute and Convalescent Phase*

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Synopsis and Abstract

Carbohydrate and lipid metabolism was evaluated in ten patients during the acute and convalescent phase of viral hepatitis. Although carbohydrate intolerance was demonstrated acutely, fasting glucose values were higher during the convalescent phase. Since insulin measurements were lower while fasting in the acute stage of viral hepatitis, some mechanism other than fasting hyperinsulinism must be involved. Following a glucose challenge, insulin measurements were higher acutely in response to the higher glucose levels. Acutely, human growth hormone and cortisol were elevated. Hyperlipidemia, particularly elevated triglycerides and phospholipids, was demonstrated. There was return to normal carbohydrate and lipid homeostasis following recovery from viral hepatitis.

TABLE 1: Mean Values of Liver Function Tests on Admission and During Acute and Convalescent Phase Testing for the Ten Patients with Viral Hepatitis Studied. Serum Glutamic Oxaloacetic Transaminase (SGOT) and Alkaline Phosphatase (Alk PO_4) Were Measured in International Units. Bilirubin, both Total and Direct, (Bili-T/D) was Measured in mg/dl.

	SGOT	Alk PO_4	Bili-T/D
Admission	1442	87	6.2/4.1
Acute phase	338	79	7.3/4.6
Convalescent phase	25	29	.70/.24

Introduction

The importance of the liver in carbohydrate and lipid metabolism is well appreciated. The literature is replete with documentation of deranged metabolism in chronic liver disease. Since patients with chronic liver disease frequently have disease outside of the liver, this model is less than ideal to study the effects of an injured liver on body metabolism. A better model would be to study the patient with liver disease and then again after full recovery, thus using the patient as his own control. Such an opportunity was provided in this prospective study in which patients with acute viral hepatitis were studied once they had stabilized to the point that they could consume a conventional hospital diet for three days and then studied again after complete recovery from the viral hepatitis. Carbohydrate intolereance and hyperlipidemia occurred acutely. Hormones including insulin, cortisol, and human growth hormone were also evaluated acutely and following complete recovery. Possible mechanisms for altered metabolism in liver disease are discussed.

Materials and Methods

Ten male patients (mean age 24.8 years, range 21-32) were studied during the acute and convalescent phase of viral hepatitis. At least one of the authors examined each patient upon admission to the hospital. Each patient gave a history and demonstrated physical and laboratory findings characteristic of viral hepatitis. None of the patients was receiving medications or had been exposed to toxins known to cause liver disease. None had a history of liver disease or drank alcohol excessively. Each patient recovered completely during the hospital course, which did not exceed six months. No patient was given glucocorticoids. No patient developed anemia or other complications of viral hepatitis. Liver function studies were performed at the time of admission. As soon as the patient was able to eat a standard hospital diet (3000 calories) for at least three days, further testing was performed. Liver function was again assessed at this time. Oral glucose tolerance tests were performed in the conventional manner using 75 gm of Glucola®.[1] Intravenous glucose tolerance tests were performed by injecting 25 gm of dextrose in 50% solution over a three-minute period. Fat tolerance testing was performed according to Havel.[2] Laboratory determinations included glucose,[3] immunoreactive insulin,[4] human growth hormone,[5] triglyceride,[6] phospholipid,[7] cholesterol,[8] cortisol,[9] free fatty acids,[10] and lipoprotein electrophoresis.[11] After the patients had recovered fully, studies were repeated. All acute phase testing was, as was convalescent phase testing, completed within a 48-hour period.

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or as necessarily reflecting the views of the Medical Department of the Navy or the Naval service at large.

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Results

Recorded in Table 1 are mean values of liver function tests performed at the time of admission, at the time acute phase studies were performed, and at the time convalescent phase studies were performed. Serum glutamic oxaloacetic transminase (SGOT), alkaline phosphatase, and direct and indirect bilirubin were distinctly abnormal both on admission and at the time of acute phase testing. Serum ammonia was measured in several patients at the time of acute phase testing and was normal. At the time of convalescent phase testing liver function studies were normal with the exception that two patients had a minimally elevated alkaline phosphatase and one patient had a SGOT 6 mg/dl above normal.

Table 2 gives the results of acute and convalescent liver function tests and serum lipids in the ten patients studied with viral hepatitis. Serum glutamic oxaloacetic transaminase, alkaline phosphatase, and bilirubin, both total and direct, were significantly higher ($p < .001$) during the acute phase compared to the convalescent phase. Acute phase triglycerides and phospholipids were approximately twice as high as during the convalescent phase and exceeded the normal values for this laboratory. The differences were significant ($p < .01$). Serum cholesterol was higher ($p < .1$) during acute phase testing than during convalescent phase testing but did not exceed the normal values for this laboratory. The triglyceride findings were consistent with endogenous hypertriglyceridemia in that lipoprotein electrophoresis demonstrated increased levels of pre-betalipoproteins in the patients tested.

The results of oral glucose tolerance testing during the acute and convalescent phase appear in Table 3 and Figure 1. The differences are significant ($p < .02$) except at 30, 120 and 180 minutes. During acute phase testing peak glucose values were of greater

TABLE 2: Acute and Convalescent Liver Function Tests and Serum Lipids in Patients with Viral Hepatitis. Serum Glutamic Oxaloacetic Transaminase (SGOT) and Alkaline Phosphatase (Alk PO_4) were Measured in International Units. Bilirubin, both Total and Direct, (Bili-T/D), Triglycerides (TG), Cholesterol (Chol), and Phospholipids (PL) were Measured in mg/dl.

	Acute						Convalescent					
Patient	SGOT	Alk PO_4	Bili-T/D	TG	Chol	PL	SGOT	Alk PO_4	Bili-T/D	TG	Chol	PL
WA	102	125	4.0/2.7	83	204	240	11	29	.8/.35	70	220	234
AM	170	71	6.2/3.6	89	146	165	40	30	1.0/.3	91	131	158
ES	590	63	1.7/.75	135	312	648	22	39	.9/.5	69	191	206
DB	350	101	13.4/8.3	148	269	484	35	33	.8/.5	58	183	153
RW	125	100	12.8/7.2	313	324	480	15	43	.7/.1	73	140	155
JH	300	35	1.0/.35	98	174	197	20	17	.3/.1	62	205	212
WC	140	70	9.6/6.2	235	195	318	46	30	.6/.25	105	173	188
JM	890	85	12.4/9.3	269	165	318	24	24	.9/.2	70	124	158
KS	300	63	4.3/1.9	121	142	196	21	25	.7/.05	127	168	229
FM	415	81	7.2/5.4	222	171	284	14	23	.3/.05	85	161	203
MEAN	338	79	7.3/4.6	171	210	333	25	29	.70/.25	81	170	190
SEM	78	8	1. 5/1.0	26	21	50	4	2	.08/.05	7	10	10

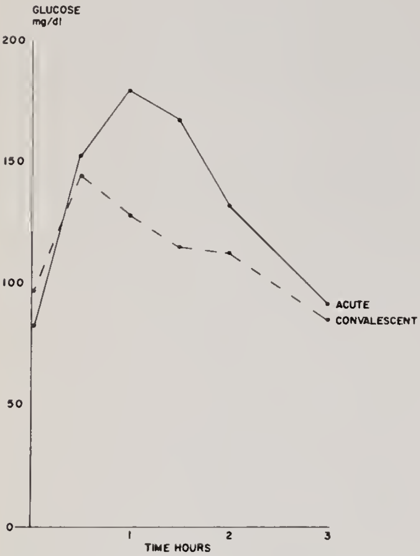

FIG. 1. Mean results of acute and convalescent oral glucose tolerance testing in patients with viral hepatitis.

magnitude and occurred later than during convalescent testing consistent with disturbed carbohydrate tolerance during viral hepatitis. The mean glucose values during convalescent phase testing were strikingly similar to values obtained when 25 normal men of comparable age were tested with Glucola® by two of the authors.[1] Three of the patients with viral hepatitis underwent intravenous glucose tolerance testing (Table 4). The K_g values were normal and not significantly different between acute and convalescent phase testing. It is well recognized that intravenous glucose tolerance testing is less sensitive than oral glucose tolerance testing in demonstrating carbohydrate intolerance.

Insulin values were higher during the acute phase as seen in Table 5 and Figure 2. These differences were significant at 30 and 90 minutes ($p < .05$). However, fasting insulin values were lower during the acute phase as were fasting glucose values.

Human growth hormone measurement, while fasting during the acute phase, tended to be higher than during the convalescent phase (Table 6).

Following a fatty meal, serum triglycerides were higher during the acute phase compared to the convalescent phase (Table 7 and Figure 3). Differences were significant ($p < .05$) except at six and eight hours. The fat tolerance tests simply showed that postprandial triglycerides are higher when fasting levels are increased. Fat tolerance was not impaired.

Table 8 and Figure 4 demonstrate 8 AM and 8 PM plasma cortisol values during the acute and convalescent phase. At both times plasma cortisol levels were significantly higher ($p < .02$) during the acute phase compared to the convalescent phase.

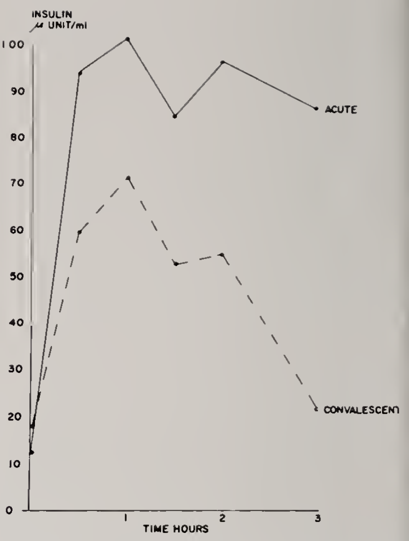

FIG. 2. Mean results of acute and convalescent insulin measurement during oral glucose tolerance testing in patients with viral hepatitis.

Free fatty acids were measured during oral glucose tolerance testing in two patients (Table 9). The sampling

TABLE 3: Acute and Convalescent Oral Glucose Tolerance Tests in Patients with Viral Hepatitis. Glucoses in mg/dl

Patient (age–yrs)	Acute–Time (minutes)							Convalescent–Time (minutes)						
	F_1	F_2	30	60	90	120	180	F_1	F_2	30	60	90	120	180
WA–32	85	86	185	290	285	172	62	94	96	170	132	118	110	65
AM–21	90	90	142	158	122	134	107	94	90	117	107	120	95	73
ES–22	87	87	149	161	137	126	78	91	91	130	144	95	121	78
DB–31	98	96	198	250	227	149	76	103	101	173	180	120	118	64
RW–21	80	85	103	119	126	108	85	88	92	118	108	94	109	106
JH–26	68	72	126	119	114	115	81	84	–	141	72	115	106	70
WC–27	56	47	131	201	186	119	152	99	99	156	197	169	128	120
JM–21	70	70	158	176	174	93	79	128	127	170	105	110	125	114
KS–21	101	96	158	191	216	197	129	85	91	133	137	150	110	76
FM–26	88	92	182	144	100	103	72	90	88	140	106	62	94	86
MEAN	82	82	153	181	169	132	92	96	97	145	129	115	112	85
SEM	4	5	9	17	19	10	9	4	4	7	12	9	4	7

TABLE 4: Intravenous Glucose Tolerance Testing in 3 Patients with Viral Hepatitis

	K_g	
	Acute Phase	Convalescent Phase
RW	2.23	2.17
JH	1.07	1.04
WC	1.21	1.40

was too small to demonstrate statistically significant data.

Discussion

The increased incidence of carbohydrate intolerance in patients with chronic liver disease is well recognized. Megyesi et al[12] suggested that chronic liver disease produced endogenous insulin resistance and hyperinsulinism. Over a period of time beta-cell decompensation occurred and diabetes mellitus developed. Such a mechanism could not explain carbohydrate intolerance during the acute phase of viral hepatitis. Berkowitz et al[13] studied ten patients with hepatitis. Nine demonstrated diabetic glucose intolerance during the acute phase. Repeat studies following the resolution of the jaundice demonstrated normal glucose tolerance in seven of the nine previously abnormal patients.

Carbohydrate intolerance was demonstrated clearly in our patients during the acute phase of viral hepatitis. There was full recovery of glucose homeostasis during the convalescent phase. Despite the presence of carbohydrate intolerance during the acute phase, fasting glucose values were lower during the illness than following recovery. Felig et al[14] reported similar findings in viral hepatitis. Liver biopsy demonstrated decreased glycogen content and the hyperglycemic response to glucogen was reduced. It was postulated that impairment in hepatic glycogen production and gluconeogenesis lead to fasting hypoglycemia. As we did (Table 5 and Figure 2), they found that fasting insulin levels were generally decreased and thus fasting hyperinsulinism could not be offered to explain the low glucose values during the acute phase of viral hepatitis. Impaired glycogen storage leading to hyperglycemia with normal insulin response to the higher glucose levels following a carbohydrate challenge

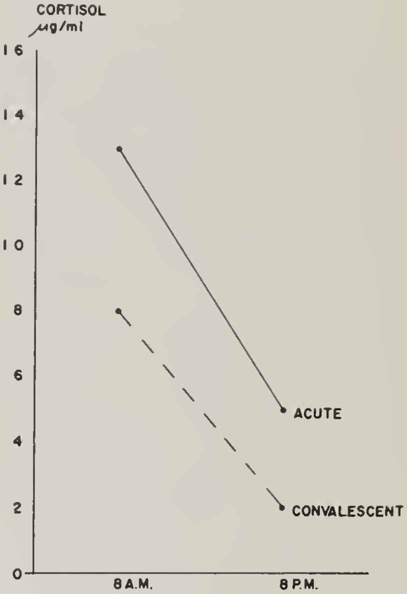

FIG. 4. Mean plasma cortisol measurements during the acute and convalescent phase of viral hepatitis.

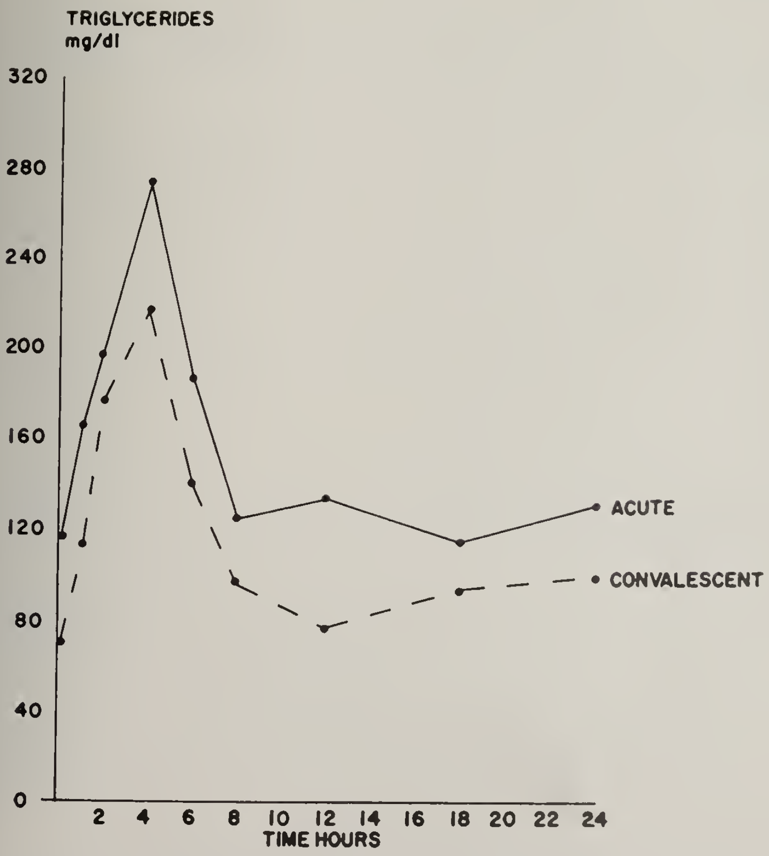

FIG. 3. Mean serum triglyceride determinations during fat tolerance testing in patients with viral hepatitis during the acute and convalescent phase.

offers an attractive explanation for the carbohydrate intolerance demonstrated during the acute phase of viral hepatitis.

Both HGH and cortisol were elevated acutely. During the acute phase HGH lowering in response to a carbohydrate challenge was appropriate. This finding has been reported previously.[15] Even though cortisol values were higher during the acute phase compared to the convalescent phase in our patients there was an appropriate diurnal variation. Viral hepatitis may provide "stress" which is known to elevate both HGH and glucocorticoids.

Serum lipids have been studied in both chronic and acute liver disease.[16-19] Generally, hyperlipidemia is more prominent in acute than chronic liver disease. In hepatitis triglycerides and cholesterol were the lipids most frequently elevated. In our patients triglycerides and phospholipids were twice as high acutely, whereas cholesterol was only moderately elevated acutely compared to convalescent phase studies. The fasting hypertriglyceridemia was consistent with endogenous hypertriglyceridemia. The fat tolerance tests showed that dietary fat was handled normally during the acute phase of viral hepatitis.

TABLE 5: Acute and Convalescent Insulin Measurements (μ unit/ml) After Oral Glucose Tolerance Testing in Patients with Viral Hepatitis

	Acute–Time (minutes)							Convalescent–Time (minutes)						
Patient	F_1	F_2	30	60	90	120	180	F_1	F_2	30	60	90	120	180
ES	15	–	79	102	83	92	–	18	20	63	98	30	78	20
JH	10	–	105	70	78	133	49	12	–	–	52	94	50	10
WC	13	14	99	131	95	52	103	20	13	57	66	35	37	33
MEAN	13	14	94	101	85	92	76	17	17	60	72	53	55	21
SEM	1	0	8	18	5	23	27	2	4	3	14	21	12	7

TABLE 6: Acute and Convalescent Human Growth Hormone (HGH) Determination During Oral Glucose Tolerance Testing in Patients with Viral Hepatitis. HGH was Measured in μg/ml

	Acute–Time (minutes)							Convalescent–Time (minutes)						
Patient	F_1	F_2	30	60	90	120	180	F_1	F_2	30	60	90	120	180
WA	5	6	6	6	5	5	–	5	–	3	4	4	6	50
AM	–	50	21	10	8	8	12	–	8	7	6	6	7	–
ES	–	–	4	4	4	4	–	4	3	4	5	5	5	4
DB	–	5	3	5	4	5	28	6	5	6	6	5	6	35
RW	–	24	14	12	13	32	9	6	5	6	5	5	5	4
JH	7	–	6	6	10	7	7	–	–	5	22	9	7	–
WC	10	12	9	9	7	21	5	–	–	2	6	5	–	–
JM	12	–	11	11	8	9	14	5	4	5	6	33	69	33
KS	28	28	11	7	6	6	6	7	6	6	6	6	7	7

TABLE 7: Acute and Convalescent Fat Tolerance Tests in Patients with Viral Hepatitis. Serum Triglycerides were Measured in mg/dl. Normal Values are for Our Laboratory are Included.

	Acute–Time (hours)									Convalescent–Time (hours)								
Patient	F	1	2	4	6	8	12	18	24	F	1	2	4	6	8	12	18	24
Normal										100	117	166	259	214	159	77	–	–
WA	84	131	185	311	125	101	159	118	140	72	123	218	327	225	85	132	93	128
AM	82	163	218	318	196	74	77	56	92	72	173	281	334	139	147	69	77	98
ES	119	144	181	264	214	137	140	98	107	69	101	106	158	100	64	65	53	70
DB	121	179	197	302	182	131	134	143	145	56	89	184	160	143	143	70	57	–
FM	186	205	213	186	167	174	158	145	172	85	83	87	96	96	55	53	64	60
MEAN	118	164	199	276	177	123	134	112	131	71	114	175	215	141	99	78	69	89
SEM	19	13	7	24	15	17	15	16	14	5	16	36	49	23	19	14	7	15

TABLE 8: Acute and Convalescent Plasma Cortisol Determinations (μg/ml) in Patients with Viral Hepatitis

	Acute		Convalescent	
Patient	Cortisol-8 AM	Cortisol-8 PM	Cortisol-8 AM	Cortisol-8 PM
Normal	5-25	<10		
WA	16.0	7.1	8.4	2.0
AM	7.5	–	6.8	–
ES	12.7	4.4	6.6	1.4
DB	12.6	4.0	6.8	1.9
KS	14.0	4.1	10.0	2.4
MEAN	13	5	8	2
SEM	1.4	.7	.7	.2

Free fatty acid levels suppressed normally following a carbohydrate challenge both during the acute and convalescent phase.

The most gratifying information obtained from this study is that, even though deranged carbohydrate and lipid metabolism may occur during the course of viral hepatitis, recovery from the hepatitis includes a return to normal carbohydrate and lipid homeostasis. Whether similar recovery can occur in other forms of liver disease remains to be elucidated.

TABLE 9: Free Fatty Acid Measurements (MEq/1) During the Acute and Convalescent Phase of Viral Hepatitis in Two Patients

	Acute–Time (hours)							Convalescent–Time (hours)						
Patient	F_1	F_2	30	60	90	120	180	F_1	F_2	30	60	90	120	180
ES	.31	.32	.27	.20	.22	.24	.26	.31	.32	.38	.31	.29	.27	.25
DB	.59	.56	.42	.33	.29	.28	.31	.33	.32	.23	.22	.21	.20	.23
MEAN	.45	.44	.35	.27	.26	.26	.29	.32	.32	.31	.27	.25	.24	.24

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Review of the Medical Management of Acute Variceal Bleeding from the Esophagus

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Introduction

The management of patients with acute bleeding from the gastrointestinal tract is often a frustrating, time consuming, and futile exercise. Such patients often enter the hospital emergency room with a history of hematemasis or melena, are referred to the medical service and, depending upon their condition and the rate of hemorrhage, may be transferred to the surgical service for definitive repair. The scope of this paper will be limited to a review of management of acute bleeding from esophageal varices in those patients who have not been deemed candidates for surgery.

Development

The advent of definitive diagnosis of bleeding from esophageal varices came with development of roentgenographic examination techniques. In 1928 Wolf, a German (cited by Kaplan), was the first to recognize the appearance of esophageal varices on a roentgenogram. According to Kaplan the diagnosis previously was made by autopsy. Until the advent of balloon tamponade, introduced by Westphal in 1930, little could medically be performed to stem acute esophageal bleeding from varices.[1]

Early definitive management of such patients included the administration of coagulative drugs parenterally or tannic acid locally via the esophagoscope.[1] The earliest use of esophageal tamponade in this country was performed in 1947 under the direction of Rowntree[2] at the Nautilus Veterans' Administration Hospital. His device consisted of a Miller-Abbot tube with a Latex bag attached distally. The hollow tube allowed for gastric lavage after placement of the bag in the esophagus with expansion to compress any varices. The device was made commercially available by the George P. Pilling and Son, Co. of Philadelphia.

The next use of tamponade was by Tocantis[3] at the present Thomas Jefferson University in Philadelphia using one of the Rowntree tubes. Of passing interest one may note that the discussion subsequent to Tocantis' article, read before the 1947 meeting of the American Medical Association, makes heavy emphasis on the use of sclerosing therapy of the bleeding varices, a treatment still in use[4] but seldom recommended, while the pros and cons of balloon tamponade were ignored.

The use of tamponade caught on and continued in the hands of Kenamore[5] (1949) who coated the Rowntree balloon with thrombin to aid in the cessation of bleeding.

Patton[6] later designed a double ballooned tube for compression of both the esophagus and cardia of the stomach. Sengstaken and Blakemore[7] (1950) designed and used their now famous bi-ballooned triple lumen tube prior to Patton's 1949 publication, for use in patients prior to portocaval shunt procedures. The production of the refined Sengstaken device and the meticulous instructions of the authors provided a definitive method of controlling hemorrhage and is currently in widespread use as the primary medical management of bleeding esophageal varices.

Bennett[8] reviewed some major complications inherent in the use of tamponade. Particularly he notes the possibility of balloon produced asphyxia, failure of both balloons to deflate properly, esophageal or gastric necrosis secondary to ischemia, and the chance of fluid accumulation in the esophagus with subsequent asphyxia. Nevertheless, in 1952 Reynolds[9] advised "routine use of balloon tamponage in suspected variceal bleeding" for use in hemorrhage control and differential diagnosis of hematemasis.

The routine use of balloon tamponade today, although useful, is not considered to be an innocuous procedure. Conn[10] cautions:

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> "Emergency treatment of variceal hemorrhage in this series was based primarily on tamponade with the Sengstaken-Blakemore tube. Although all of the well known difficulties with this device were encountered from time to time, we have been encouraged to depend on it as the most reliable emergency approach."

Other techniques developed to aid in the acute management of variceal bleeding include Nachlas'[14] gastric ballooned tube with a lumen for esophageal lavage and the use of hypothermia introduced by Wangensteen[15] in 1958 and modified by Small and Brick in 1964.[16]

The underlying principle in the use of hypothermia in the range of 17 to 20 degrees Centigrade as originally introduced in 1958 was to depress gastric secretion and control "massive hematemasis of acid-peptic origin."[15] Small has used a less expensive apparatus utilizing equipment readily available and has extended his method to include gastro-esophageal tamponade while cooling via the balloon.[17]

Vasopressin (Pitressin), a posterior pituitary gland extract, was first used for the control of bleeding varices by Kehne in 1956.[18] The drug causes constriction of the vascular system which is not blocked by nerve section, atropine, or adrenergic blockers.[19] Kehne *et al.* demonstrated a 25.3% decrease in portal pressure using intravenous Pitressin in normal dogs. Elevated portal pressure created by partial obstruction of the inferior vena cava in dogs showed a 33% average decrease in pressure lasting for approximately one hour. Kehne theorizes the mechanism for the lowered pressure to be splanchnic vasospasm. The use of 10 to 20 U of Pituitrin (S) controlled hemorrhage in two patients; however, he cautions the drug should be an adjunct to emergency therapy and is not a substitute for tamponade.

Schwartz *et al.*[20] in 1959 used intravenous Pituitrin (20U) in eleven patients bleeding acutely from esophageal varices. In nine of these patients 22 episodes of hemorrhage were quelled. They also used the drug in nine patients during portacaval or splenorenal anastomosis procedures and in two patients during trans-esophageal ligatation of bleeding varices. In those instances bleeding was controlled during the normally bloody procedures. Measurements of portal pressures after infusion with Pituitrin showed a decrease of portal pressure to the level obtained with subsequent shunt procedures as measured at the time of surgery. The use of Pituitrin is recommended by these authors as an initial therapy for variceal hemorrhage in light of the known disadvantages over balloon tamponade.

Shaldon and Sherlock[21] administered intravenous Pitressin to eight patients bleeding from esophageal varices. Portal pressures were recorded in five of their patients via percutaneous splenic puncture and monitoring of the intrasplenic pressure. A mean decrease from 26 mm Hg to 14.5 mm Hg (46%) was demonstrated. Prior to infusion, these patients required transfusions of an average of 2500 ml. of blood over an average of 16 hours (range 6 to 72 hours). Following infusion, bleeding stopped within one hour. Four of the eight patients expired, death being attributed to the degree of liver failure and not as a complication of the drug infusion. Pitressin is recommeded by these authors as a alternative to Sengstaken's esophageal compression.

Use of intravenous Pitressin was evaluated by Drapanas[22] on a series of dogs. The drug in doses of 4-20 U (0.5U/kilogram) reduced portal vein and hepatic arterial blood flow with a 51% decrease of total hepatic blood flow below normal control values. Cardiac output reduction averaged 58%, both effects lasting forty to sixty minutes. Bradycardia occurred along with cardiac arrythmias, ventricular extrasystoles and first and second degree heart block. The study corroborated the known action of pitressin to produce generalized vasoconstriction with reduction of cardiac output, coronary blood flow, hepatic, and intestinal flow.

In 1963 Nusbaum,[23] at The Harrison Department of Surgical Research, published his first animal study on the radiologic demonstration of occult bleeding from the gastrointestinal tract. He concluded that:

> "preoperative selective arteriography of the celiac, superior mesenteric, and inferior mesenteric arteries fulfilled the criteria of simplicity, accuracy, and low morbidity."

Correspondence from Nusbaum's laboratory published in 1965[24,25] states the clinical criteria which were fulfilled by patients subsequently studied:

1. Active bleeding was clinically demonstrable.
2. Conventional techniques for diagnosis were valueless.
3. The decision to operate had been established so the procedure was a preoperative study.

This diagnostic technique was useful in demonstrating bleeding sites in four out of eight patients, one of whom was bleeding from gastric varcies. The complication rate incurred by this procedure was shown to be attributable to the patients' underlying disease and not the procedure.[26]

The next logical step in the medical management of esophageal bleeding was the combination of Kehne's use of intravenous pituitrin with Nusbaum's selective angiography of the mesenteric vessels. In August 1968, Nusbaum *et al.* published their work entitled "Control of Portal Hypertension by Selective Mesenteric Arterial Infusion."[27] The technique described entailed selective mesenteric arteriography to locate the bleeding site with subsequent infusion of pituitrin in low doses (0.2 pressor U/ml/ minute of infusion). Infusion was carried out in a series of animals producing a 58% decrease of blood flow in the superior mesenteric artery. The authors leave the catheter in place for continued infusion if necessary.

Infusion of pitressin was carried out on two patients suffering from acute upper gastrointestinal bleeding from portal hypertension and varices. One case was successfully controlled allowing for a subsequent semielective portacaval shunt procedure, while the second patient needed balloon tamponade along with drug infusion for hemorrhage control.

The systemic effects of pitressin demonstrated by Drapanas have been alluded to by Rosch.[28]

> "With selective arterial infusion, the doses of vasoactive drugs may be kept to a minimum, thus limiting effects only to infused vessels and minimizing unfavorable effects in the systemic circulation."

As with earlier methods used in the medical management of bleeding from esophageal varices, clinical investigators today are slow to heed the advice of controlled laboratory studies. Investigaors like Drapanas in 1960 or Graybriel[29] in 1941 are rarely footnoted in clinical trials using pitressin. Continued use of pitressin in gastrointestinal bleeding by Rosch has failed to produce major systemic alterations in his patients.[30] Conn[31] has controlled bleeding in 35 patients, about 10 of whom had bleeding esophageal varices. Seventy-nine percent of the variceal bleeding patients were controlled in 15 episodes of hemorrhage. Complications encountered by Conn included:

Cardiac arrest	1
Respiratory arrest	1
Bradycardia	5
Hypertension	2
Reactive erythema	4
Angina pectoris	1
Intestinal necrosis	1
Peripheral embolism	1
Arterial bleeding	2
Catheter migration	3
Catheter clotting	2

There were no fatalities with these complications in his total series. Conn, perhaps with the insight of Bennett (1950) and his early warnings on the use of the Blakemore tube, has brought to light a number of serious complications not heretofore mentioned.

The sparcity of reported complications is not likely to be attributable to the low doses of pitressin infused locally, even though "bolus" intravenous therapy produces drug concentrations with a higher risk. A recent study by Millette[32] has shown that 0.2 U/ minute of pitressin infused into the superior mesenteric artery of eight cirrhotics produced systemic responses such as a lowering of pO_2, femoral pressure and cardiac output. Nevertheless, double blind controlled studies relating the efficacy of selective arterial infusion versus intravenous "bolus" therapy and the associated complication rates have not been done.

Discussion

Acute variceal bleeding from the esophagus has no real animal model. The combined complications of shock, hepatic coma, renal shutdown, and cardiorespiratory arrest can be individually studied in the laboratory. However, clinically these problems are often faced in the same patient, along with the possibility of catastrophe secondary to treatment. The value of using vasoactive drugs in managing variceal hemorrhage has been clinically demonstrated. An evaluation of the precise indications of such therapy is needed in light of the possible complications. As with the earlier use of the Sengstaken-Blakemore tube, the use of selective vasoconstriction today in managing variceal hemorrhage has many pitfalls which are slowly being recognized.

The physician faced with treating a patient hemorrhaging from esophageal varices today also has available the technique of endoscopy to assist in precise diagnosis.[32] The effectiveness of these diagnostic and treatment methods used independently or jointly should, at this time, undergo clinical investigation to determine the optimal choice of the alternative techniques available for each patient. Perhaps the ultimate solution in managing such patients lies in a joint team effort combining the specialties of internal medicine, gastroenterology, radiology, and surgery.

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The Relationship of Hepatitis Associated Antigen (Australia Antigen) and Chronic Active Hepatitis—Review of Current Literature

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Key to Abbreviations Used

HAA	Hepatitis Associated Antigen (Australia Antigen)
HAA-AB	Hepatitis Associated Antigen-Antibody Complex
AVH	Acute Viral Hepatitis
CAH	Chronic Active Hepatitis
AIH	Acute Infectious Hepatitis
ANA	Anti-Nuclear Antibody
AMA	Anti-Mitochondrial Antibody
ASMA	Anti-Smooth Muscle Antibody
SGOT	Serum Glutamic acid Oxaloacetic Transaminase
PBC	Primary Biliary Cirrhiosis

Introduction

Clinicopathologic Discussion

Chronic active hepatitis is classically described as an inflammatory process of the portal area, of predominantly mononuclear cells, which invade the periportal parenchymal cells causing hepatocellular hydropic degeneration and necrosis. Fibrosis, either reactive to inflammation or from condensation of the liver reticulin network, extends from the portal areas isolating the hepatocytes into disorganized clusters of regenerating cells. Cellular regeneration is eventually outstripped by the fibrotic process, and a cirrhotic liver is the final outcome, heavily scarred and shrunken. Fatty change is not seen to occur[1,2].

The onset of CAH is usually insidious, but about one-third of the cases have an abrupt onset resembling AIH, the difference being noticed only with the persistence of jaundice, malaise and fever over several months duration. The patient often appears to be in good nutritional status; and with the insidious type of onset, the only complaints often are two or more of the following: slowly progressing jaundice, anorexia, hepatomegaly, persistent fever and arthralgia, vague abdominal pain, and any of several patterns of skin rash. There are recurrent episodes of active disease when these complaints may become exaggerated, accompanied by marked fatigue, purpura, and liver tenderness. Liver function tests and serum enzymes will be abnormal during these episodes, and in between may return to relatively normal levels[1,3].

About 50% of cases show manifestations of systemic dysfunction and immunologic imbalance not related to the liver, thus suggesting that CAH may be a pansystemic disorder. Most of the associated diseases are the so-called autoimmune ones, and include arthralgia and rheumatoid disease, lupoid glomerulonephritis, lupus-like skin rashes, Hashimoto's thyroiditis, Coomb's positive hemolytic anemia, polyneuritis, pulmonary fibrosis, and thrombocytopenia. Endocrine disorders are also common and include Cushingoid habitus, acne, obesity, hirsutism, amenorrhea in females, and gynecomastia in males[1,4].

Liver function tests vary during the inactive stage, but during the active stages, there will be elevated serum bilirubin, SGOT, and globulins. Various serologic tests also will often be positive during the course of the disease, and these include positive LE cells in about 15% of cases, ANA in about 50% of cases, AMA in about 28% of cases, and ASMA in about 50%[1,3]. The significance of these antibodies is not understood since they are neither organ nor species specific, and may simply be a result of liberated cell debris accompanying a chronic destructive process[3].

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Mortality is about 65% during the first five years, but after surviving this period, the prognosis is somewhat better for long-term survival[3]. The disease may become inactive after many years, but the end stage in most cases is cirrhosis, usually complicated by GI hemorrhage, hypersplenism, ascites, prolonged jaundice, and terminally, hepatic coma due to hepatocellular failure. Biopsy is needed for diagnosis, and also for prognosis, the most important sign being the amount of fibrosis which is a marker for the cirrhotic process[2].

The previous discussion has concerned the aggressive type of CAH. There is a benign type, called persistent, in which the inflammatory changes are confined to the portal areas and do not invade the surrounding parenchyma. Clinical signs and symptoms are mild or absent. Biopsy may show bile duct proliferation, but there is no progression to cirrhosis and no treatment is required[2]. Unless specified, the term CAH will refer to the aggressive type, which is the clinically recognized and significant entity.

The basic cause(s) of CAH is yet to be discovered, however two theories which predominate the research literature at present are viral etiology and immunologic dysfunction. In neither case has significant direct evidence been accumulated.

An altered immune reaction is suggested by the frequent association with other autoimmune disease, concomitant hypergammaglobulinemia, various and variable serologic test reactions, plasma cell infiltration of the portal areas, clinical and laboratory response to immunosuppressive therapy, and similar pathologic changes seen in experimentally induced immunologic liver damage in animals[3].

A viral etiology is suggested by a clinical onset similar to that of AIH in about one-third of cases; history of contact with a case of AIH; evidence that AVH is a systemic disease with demonstrable pathologic changes in many organs; pathologic changes in early CAH similar to those in AVH; increasing reports of cases of AVH progressing to post necrotic cirrhosis; and the findings that many diseases thought to be genetic or immunologic at one time are now showing isolation of viral agents[3].

Evidence for Viral Etiology

Several investigations have been carried out on the relation of HAA to CAH, with varying results and interpretations. The association of HAA and AVH is now well known and accepted. The persistence of HAA in some of these patients, however, is not well understood[4].

One theory investigated is that CAH is a viral disease. Although no virus has yet been found in the liver of patients suffering from CAH, viral injury may be the cause of the inflammatory reaction. Kaplan and Grady[5] examined the sera of 56 patients which they divided as follows: Persistent CAH 10 patients, aggressive CAH 24, aggressive CAH with positive LE cell tests (lupoid) 10 patients, PBC 10, with two patients showing features of both persistent and aggressive CAH. Their methods of HAA detection were immunodiffusion, immunoelectro–osmophoresis, and complement fixation. No significant differences were found among the results which were as follows:

Positive tests for HAA[5]

	ID	IEOP	CF	Total Patients
Persistent CAH	8	8	7	10
Aggressive CAH	1	0	2	24
Lupoid CAH	0	0	0	10
PBC	0	0	0	10
mixed CAH	1	1	1	2

ID = immunodiffusion IEOP = immunoelectro-osmophoresis CF = complement fixation

The data suggest that persistent CAH is related to prolonged infection with the agent producing HAA. Nine of these ten patients had a history of exposure to other hepatitis patients, use of contaminated needles, or recent blood transfusions. The aggressive type showed very little or no incidence of HAA in the sera, in contrast to other studies which have found as much as a 25% incidence[10]. This raises the possibility of an immunologically different and distinct HAA[14]. The possibility also exists that the host defenses alter the ability to detect the antigen. These patients could very well be suffering an immunologic dysfunction as suggested by the high prevalence in the patients in this study (38%) and elsewhere of systemic autoimmune disease including thrombocytopenia, hemolytic anemia, colitis, and thyroiditis. The possibility of immune complex with HAA causing the presence of the antigen to be masked is raised, but pursued no further. Such complexes could not be detected with the methods used, but might still be present, and could be the source of the inflammation. No patients with PBC were found to harbor HAA[5].

Nielson *et al* believe that genetic susceptibility of an individual to persistence of HAA is in some way a causative factor leading to CAH. As previously mentioned, the association of HAA and AVH is now well established, but the significance of the persistence of the antigen in some of these patients is not. Usually the HAA disappears within four to five weeks of the onset of symptoms in AVH. Fifty-seven patients with AVH diagnosed by biopsy were followed with subsequent biopsy and serum studies. Ten patients with persistent HAA were followed for 26 months and 47 without persistent HAA were followed for 19 months. Out of a total of 253 patients seen for AVH, 112 or 44% had HAA-88 transitorily, 11 for at least 11 months, with 13 lost to follow-up. The eleven with persistent HAA represent 4.3% of the entire AVH group, which approximates 3-4% of the general population which is estimated to be susceptible to persistent HAA-emia. All 11 developed CAH; eight of the aggressive type, two of the persistent type (one patient refused repeat biopsy). Of the group of 47 without persistent HAA, biopsy showed that three developed persistent CAH, three developed aggressive CAH, and one showed possible transition to a chronic state, with the remaining 40 showing regression of their disease or non-specific post AVH signs. In summary, in group I with 10 patients showing persistent HAA, 100% progressed to CAH; in group II, only 15%, none of whom showed persistent HAA in their sera, progressed on to CAH[4].

There are three groups of people who may carry HAA chronically: healthy people who never show any manifestations; people with other chronic illnesses; and people who have had a history of AVH exposure with a positive test for HAA. The first group has been found in epidemiologic studies. The second group shows some evidence of increased incidence of chronic liver disease, but the significance of these findings is unknown at present. The third group of chronic carriers, those with a history of AVH exposure, were all found by Nielson to develop CAH. Since the percentage of persistent HAA carriers in this study of 253 AVH patients closely approximates that believed to hold for the general population, and since all of the patients with persistent HAA developed CAH, Nielson's study seems to show that the development of CAH is influenced by the genetic susceptability of the patient to the persistence of HAA after an attack of HAA associated AVH[4].

Bulkley *et al*[6] investigated thirty cases of CAH at the Massachusetts General Hospital and divided the patients into three groups determined by serologic tests for HAA, ANA, and LE cells, and reported:

Serologic and Clinical Aspects of 30 CAH Patients[6]

	I	II	III
Total cases, male and female	7.7/0	9.5/4	14.10/4
Serologic tests			
HAA +	7	0	0
LE cell +	0	6	0
ANA +	0	7	0
Exposure: none	1	9	7
shared needle	2	0	1
transfusion	4	0	4
AIH	0	0	2
Onset			
abrupt	5	2	6
insideous	2	7	8
Mean age	33.9	27.1	35.3
Cirrhosis			
number	4	2	9
percentage	57%	22%	64%

Those in group I had persistent HAA titers for greater than six months, except for one who died after two months, and there was no overlap in serologic test results between groups I and II. Group III, although negative for all serum tests, cannot be said to have been negative before the diagnosis of CAH was made. The greatest differences were noted between groups I and II. Group I showed a high incidence of parenteral exposure, group II did not. Group I patients usually showed abrupt onsets, while group II suffered mainly insidious ones. Group I had a higher occurrence of cirrhosis, but this may be a reflection of age. Group I was totally male, and group II had a slight female predominance. Group II also showed a higher incidence of extra-hepatic disease, eg.–thyroiditis, arthritis, rash, and ulcerative colitis. Group I patients developed some arthritis only[6].

In this report, persistent levels of HAA were found in CAH patients with a history of parenteral exposure. HAA is also known to be transiently high in over 70% of cases of AVH of transfusion or parenteral origin. Also on record are several cases showing apparent progression (by biopsy) of apparent AVH to cirrhosis, which is not commonly thought to occur. Taken together, this evidence has lead to the theory of persistent viral infection as the pathologic mechanism in CAH[6].

Viral hepatitis is generally thought to be a self limiting disease. However it is now recognized that some people carry persistent titers of HAA antigen. In 1969 Almeida and Waterson showed what they thought to be HAA-AB complexes in the serum of a CAH patient.[11] They also found free HAA particles implying an antibody deficiency or antigen excess. The patients in group II, whose disease was found to have some historical differences from that of group I, showed associated autoimmune diseases distinct from their liver disease, as stated above. These patients all had the higher average IgG levels and serologic reactions seen in autoimmune disease. Additionally, mild inflammatory changes of the liver have been found in patients suffering diseases such as systemic lupus erythematosis, rheumatoid arthritis, and thyroiditis. The association is speculative at the present time, but does suggest some type of relationship, perhaps of an immune-complex deposition with resultant inflammatory change.

All of the patients in this study showed similar pathological, biochemical, and clinical characteristics of their disease, the only detectable difference being the serologic tests. It is conceivable that what we now call CAH is actually a spectrum of diseases with multiple etiologic factors, a better understanding of which would aid in assessing prognosis and planning therapy[6].

Evidence for Immunologic Dysfunction

Prince *et al*[7] believe that HAA-AB complex deposition is not a pathogenetic factor in CAH. In their study, they found that 25% of all HAA carriers had elevated SGPT, and of this group, only 25% were found to have CAH by biopsy. Using hemagglutination techniques, they found that HAA-AB complexes, when present, did not correlate well with the presence of chronic liver disease. When present, they felt it to be an unrelated phenomenon. They cite the work of Nowoslawski in which he demonstrated an Arthrus-like reaction in the skin of rabbits with what he presumed to be HAA-AB complexes[13]. However, an Arthrus reaction evokes a predominantly neutrophilic response, and the liver inflammation found on biopsy is of monocytes and plasma cells. The following is offered as evidence for a cell mediated type of immune injury: 1. CAH can proceed to a cirrhotic state even with low levels of immunoglobulins; 2. immunosuppression produces clinical improvement and has its effect primarily on cell mediated responses and not on antibody production: 3. There is evidence that immune-competent lymphocytes recognize “self” liver cells in cases of CAH, possibly because of surface antigens altered by a virus. The immune response may be a normal response of the host to try to end an infection, but if the response is not strong enough, a chronic carrier state results with continued cell injury leading to eventual cirrhotic changes[7].

Dudley, Fox, and Sherlock[8] have evidence which they believe shows that the liver injury is a result of variations in immune responsiveness to HAA, and is not directly related to the titers of HAA present. They studied 87 patients with HAA in their sera for antigen titers and serum third component of complement levels. They also did similar studies on 18 patients with massive liver necrosis. The distribution of the patients was as follows:

Patient Distribution[8]

	Total	Male	Female	AVH history
AVH	37	23	14	0
HAA Carriers	12	9	3	2
Persistent CAH	13	11	2	8
Aggressive CAH	17	17	0	10
10 liver cell carcinoma	8	7	1	5

Diagnosis was by clinical course and also by biopsy in most cases, except for the AVH patients. Carriers were those with persistent HAA-emia for more than six months without serum transaminase elevations. Of the 18 separate patients with massive liver necrosis, 15 were diagnosed as fulminant viral hepatitis, four with detectable HAA. The other three were post ingestion of paracetomol, marsilid, or isoniazid[8].

A significant difference among the above groups was found for serum HAA titers. The highest values were found among the carriers, with persistent CAH patients showing the next highest values. The lowest titers were found among the aggressive CAH and carcinoma patients. This shows an inverse relationship between the severity of liver cell disease and injury and serum antigen levels. Those with AVH showed serum HAA titers ranging to both extremes. The four HAA positive patients from the group with massive liver destruction also showed low HAA levels. If the serum titer accurately reflects the amount of HAA present in the patient, then HAA probably is not directly responsible for the resultant liver cell damage. Variations, either humoral or cellular, in the patient's immune system could account for the destruction. If the humoral response is responsible, then antibody–antigen complexes in the presence of serum complement could be causative of the liver destruction via cell lysis. The greater the amount of antibody present, the less free HAA will be detected and the greater will be the liver cell destruction. Several investigators have already published reports of finding such HAA-AB complexes in patients with CAH, as has already been described. Such complexes have also been found in persistent HAA carriers with lymphoproliferative disorders in other tissues, such as kidney and arteries. For this reason serum complement levels were also studied with the expectation that they would be depressed in patients with low HAA titers and the more serious liver destruction. The measurement of serum third component of complement was within normal range in the great majority of all patients except the 18 in the group with massive liver necrosis. This group included only four with HAA-emia, and three with liver cell destruction due to toxicity, and probably reflects a decreased production rather than an increased utilization of complement for immune reactions. These results would seem to indicate that immune complex induced injury is not the pathogenetic mechanism[8].

Cellular immune response seems to offer a better explanation at this time of the destructive process. The greater the cellular response, the greater the tissue destruction via delayed hypersensitivity mechanisms, and the less the titer of measurable HAA. Defective cellular immune response may be important to the disease process. Other reports have shown that in chronic disease states such as leukemia and lepromatous leprosy, where cellular immune response is decreased, there is a higher incidence of HAA carriers[12]. In accordance with these findings are observations that several carriers in the study by Dudley *et al* had conditions which depressed their cellular immune response such as sarcoidosis or chronic renal failure. Also, one patient with aggressive CAH, when treated with prednisone, showed clinical improvement with decreased serum transaminase levels and concomitant rise in serum HAA titer. Possibly the steroid therapy repressed the injurious immune response while at the same time allowing the antigen proliferation and consequent increase of serum HAA titer[8].

Summary and Discussion

"The relation of Australia antigen to the different forms of chronic hepatitis remains to be established"[2]. In different series the incidence of HAA in CAH patients has ranged from 0% to 25%. This suggests at least two groups of CAH patients; however no histologic evidence exists for anything but a single disease entity[9].

With reference to the current literature, the following points can be made:

1. HAA persistence is significant in certain patients who develop CAH, but as yet these patients cannot be separated as a distinct clinical entity;
2. CAH has a relation to other autoimmune diseases, although the exact nature of this relation has yet to be described;
3. Cellular immune defense dysfunction offers the least objectionable explanation for a pathogenetic mechanism for CAH of an "autoimmune nature";
4. Viral etiology can be compatible with cellular immune dysfunction in much the same way that cancer is postulated to change cellular surface antigens, thus evoking an immune response to altered cells of the individual's own liver cell population.

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The Postmastectomy Lymphedematous Arm*

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Foreword

It is curious why simple procedures are so often left undone. The proverbial "ounce of prevention" is certainly a good postulate for the postmastectomy patient but, frequently, the surgeon has neglected this aspect of care. The type of early preventive and late restorative care mentioned is a model for all to follow. It takes so little time and effort and yet accomplishes much. There is another plus to this program: that is, the patient's relating to knowledgeable people. These are professionals who can look at the surgical site, palpate it and not be embarrassed, shocked, or turned away. This aids the patient in accepting the program as a routine. The more people involved in this endeavor, the easier it is for the patient to accept the situation. The therapists, through their training and experience, know the psychological impact of this surgery. The patient will many times relate better to these professionals than to the surgeon. I have seen patients who would refuse to look at their incisions but would, after a few treatments with psychological support, completely reverse their attitudes.

Having treated many of these patients in the early and late stages, I can say from experience that all mastectomy patients deserve an early introduction to this program. It is generally short and simple, and through this means, they become aware of the help that is available. If problems should arise, they can seek help early.

Introduction

Postmastectomy lymphedema causes serious problems in less than ten percent of patients. Yet, when it occurs, lymphedema is a distressing and sometimes disabling burden for the patient and a challenge to the physician. Controversy continues regarding etiology and treatment programs vary. However, it is agreed that the prevention of the postmastectomy edematous arm is far more valuable than any valiant surgical or medical procedure designed to remedy the condition once it has occurred.

Etiology

An often confusing array of etiologic factors have been advanced to explain the development of lymphedema. Prime factors appear to be: (1) unusual trauma of the axillary vessels during surgery; (2) postoperative infection of the axillary area; and (3) fibrosis following radiation therapy. Postoperative infection, signalled by localized induration and occurring even years later, as the result of burns, cuts, insect bites, severe bruises of the hand, arm and forearm, hypodermic or intravenous injection or vaccination may either initiate the process or increase the severity of preexisting lymphedema.[1]

Regardless of the specific etiology, the mechanisms producing lymphedema are essentially the same: the lymph flow from the extremity is blocked causing an increase in hydrostatic pressure. This increase in pressure leads to dilated lymph vessels and incompetent lymph valves. At the same time, there is an increase in the protein content of lymph and proliferation of fibroblasts in the tissues. And, since a lymphedematous extremity is an excellent culture medium for bacteria, resultant infection may lead to thrombosis of the lymph vessels and further blocking of lymph flow, increased lymph stasis and progressive fibrosis of the connective tissue.

Prevention

Preventive measures begin at the time of operation. Careful handling of tissues during the surgical procedure and the development of an incision that will not close directly over the axillary bundle are advised. Also, care should be taken not to disturb the clavicular portion of the pectoralis major muscle since it will provide a shelflike roof for protection of the proximal portion of the axillary vein. To prevent injury to existing structures, vein thrombosis, infection or the formation of excessive cicatrix, it is important that the physician: (1) use a sharp dissection thus avoiding the necessity for mass clamping or mass ligature; (2) handle the axillary vessels gently and carefully ligate the tributaries of the axillary vein; (3) use fine suture material. Primary skin grafting may help avoid incisional scars over the axillary vessels. Specific operative procedures designed to avoid postmastectomy edema have been described by various physicians.[2]

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Another important aid in the prevention of lymphedema is the maintenance of gravity drainage following surgery through elevation and partial abduction of the extremity. The patient's fingers and hand are raised higher than the forearm and the forearm higher than the pillow. Since this position cannot be maintained for the optimum period of six weeks, elastic compression bandaging from finger tips to shoulder is highly recommended for six weeks following surgery. Active motion and graduated exercises beginning on the first postoperative day are also helpful.[3] However, such exercises are not indicated when skin grafts have been used or when the patient has been subjected to a radical mastectomy and chest wall resection.

It is essential that the postmastectomy patient be instructed on the various measures to prevent trauma which may lead to impaired lymphatic and vascular circulation. The following written list of "dos and do nots" should be given to patients upon discharge:

1. Push cuticles back–do not cut–avoid possible infection.
2. Wear canvas gloves when gardening; wear rubber gloves when cleaning pots and pans with steel wool.
3. Wear padded gloves when reaching into oven. Avoid burns.
4. Keep watch band and jewelry loose on operative arm.
5. Keep dress sleeves loose. Avoid pressure and swelling.
6. Use unaffected arm to carry heavy purse and packages.
7. Use unaffected arm for blood pressure readings, injections, vaccination, etc.
8. Wear thimble when sewing.
9. Wash the smallest break in the skin on operative side, immediately with soap and water, and cover with a band aid.
10. Use electric razor for shaving and avoid nicks and scrapes.
11. Do not get sunburned; get tanned gradually.
12. Contact doctor if arm on operative side feels hot, is reddened or swollen.
13. Hold cigarette in the unaffected hand–avoid possible burns.
14. Keep arm elevated when sitting; do not let arm hang down by side.

Frequent follow-up is necessary to keep the patient mindful of the need for preventive action. The use of a fitted elastic sleeve and/or one of the available units which apply controlled pressure is practiced by many clinicians and although these procedures can be useful, in-depth scientific evaluation of these products is not available.

Treatment

Despite preventive measures, approximately ten percent of postmastectomy patients develop lymphedema. Present-day chemotherapy has been helpful when infection is present; surgical procedures reported in the literature designed to reestablish lymph flow generally result only in a modicum of success. However, there is recent encouraging data on the control of postmastectomy lymphedema by the transposition of the partially detached omentum beneath the superficial tissues of the chest wall to the axilla and upper arm.[4]

Nevertheless, it appears that for the present we must consider some kind of mechanical means to overcome the obstruction of fluid flow. Elastic sleeves are frequently helpful although they may be uncomfortable for the patient and they are sometimes cosmetically unacceptable. A pressure pump may be helpful in special instances under medical direction. However, if there are signs of lymphangitis (redness and streaking of the arm, with or without accompanying fever) manual manipulation of the arm is contraindicated.

Because of the prevalence of infection, some physicians give antibiotics prophylactically to all patients with postmastectomy lymphedema.[5] Antibiotics are advised in the acute phase of lymphangitis, for long-term treatment during the chronic phase, if there is any necrosis of the wound margin or fluid beneath the wound flap.[6] A low salt diet may help, at times, and the administration of dehydrating agents has been of limited assistance.

Summary

Postmastectomy lymphedema is a distressing and sometimes disabling complication which causes serious problems in less than ten percent of patients. All available preventive measures should be utilized since medical and surgical procedures are not very effective once the entity has occurred. The use of elastic sleeves and pressure pumps may be beneficial. Antibiotics are indicated in the acute phase of lymphangitis and for long-term treat-

medical society of the district of columbia
vol. 42 no. 10 october 1973

ment during the chronic phase, if there is any necrosis of the wound margin or fluid beneath the wound flap. A low salt diet and the use of diuretics may also be of assistance.

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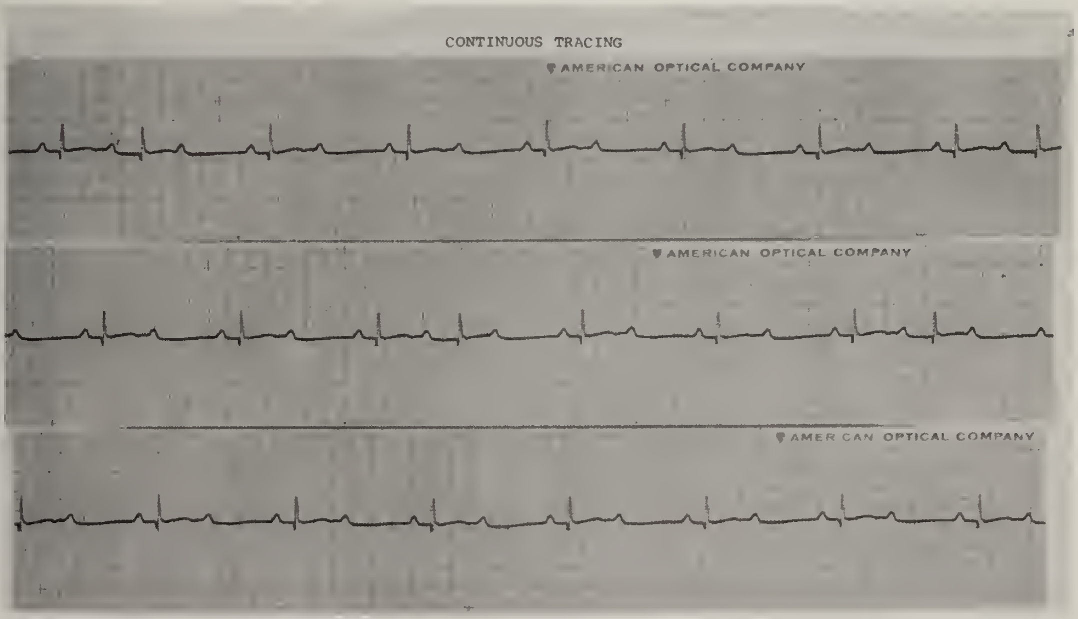
ECG PROBLEMS

HISTORY: The following is a continuous monitor strip taken from a patient in the Coronary Care Unit. He had acute chest pain earlier on the same day and 12-lead electrocardiogram showed early signs of acute inferior wall myocardial infarction. At the time this strip was obtained, the patient was not experiencing pain, but was slightly dyspneic.



(for diagnosis see page 502)

SPECIAL ARTICLE

Community Health Aspects of Water Pollution Problems

BAILUS WALKER* AND THEODORE J. GORDON†

Introduction

Dire predictions of health dangers from environmental contamination are routine in the news media and are common topics of daily conversation. Some of the allegations are sound, others are patently alarmist and exaggerated; for many important data are lacking. In the last decade, it has become clear that problems of environmental health are too urgent to be blithely brushed aside.

With the growth of technology, the problems of environmental contamination have become increasingly apparent. Electric power generating capacity has increased over 20-fold from 1920 to 1970. Rapid urban development in the past 20 years imposed increasing demands on available water supply. Many communities have fully developed all local sources of water and are dependent on the development of distant water supplies to meet future requirements.

In the District of Columbia, the Potomac River is the only source of water for the Washington Metropolitan area and will be for some time in the future. At present, the maximum daily demands on the River are about 400 million gallons per day (MGD). When the River is at low ebb, the flow or record was 388 million gallons per day (MGD). Maximum daily demands in the mid 1979's to 1984 is anticipated to be 955 MGD, a period which for supply purposes is already here.

It is a well-known fact that the District has only a two-and-one-half days' reserve supply of water, compared to a one-year supply for Baltimore and a three-year supply for New York City. This fact has been aired publicly for many years, but no action has yet been taken to correct this situation.

Although studies for developing water resources on the Potomac have been made over the past ten to fifteen years, hearings held, investigations made and conferences convened; nevertheless, significant construction to meet the ever mounting demands is limited to the Bloomington, Maryland Reservoir, now in early stages of construction, and an emergency intake structure on the upper estuary for the District, also in the early stages of construction. These will only begin to meet the water supply problem.

The Bloomington Reservoir will only increase the low flow by 142 million gallons per day. The proposed Verona and Sixes Bridges Reservoirs would increase the low flow by an additional 219 million gallons per day. Therefore the combined low flow with the construction of the three dams plus the Potomac River low flow of record would only result in a total dependable low flow of 749 million gallons per day, still far short of the anticipated 1984 requirement of 995 million gallons per day.

Only two reservoirs—Verona (near Stauton, Virginia) and Sixes Bridge, on the Monocacy River in Maryland—out of a possible six or seven dams, have been recommended to the Congress for authorization by the Secretary of the Army.

A continuous shortage of water in the Washington Metropolitan Area could lead to the rationing of water for all but essential uses, and to a building moratorium. In the meantime, the population of the area (covering the District and populous areas of Maryland and Virginia) continues to grow, with each person using more and more water.

In view of this continuing water resources problem and related issues of environmental health, it is appropriate to review relevant information on water quality and community health and provide selected references for an informed judgement on this subject.

Health Considerations

While accomplishments in the Western World have lowered the morbidity and morality rates of waterborne diseases, approximately two-thirds of the globe's population is still under serious threat to health via unsafe and inadequate water supplies. In this century, cholera has appeared in India, Ceylon, Iran, Vietnam, and China. As late as July 1971, the El Tor Strain of Cholera made a new advance across Asia, Europe, and Africa from the beginning of its most recent pandemic in the Celebes Islands. At the height of the tourist season, the Spanish Government confirmed several cases of cholera in the northeastern province of Zaragoza while thousands of Spaniards in that city waited in line to be inoculated against the disease. This disease remains unconquered and a symbol of a way of life where safe water is still an unattainable luxury.

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American communities are concerned over waterborne viral disease. This concern exists despite the fact that of the enteric-viral diseases only infectious hepatitis has been shown to be waterborne, but proving a waterborne character for infectious hepatitis has been difficult because of its prolonged incubation period and the inability to isolate and identify the causative virus. In fact the first isolation of viruses from drinking water in the U.S. was accomplished last year by Walter Mack of Michigan State University,[1] from a 100 foot well in Monroe County, Michigan. The virus isolated was serologically identified as poliovirus type 2 and probably was excreted Sabin vaccine.

The literature of the past suggested that poliomyelitis may be transmitted through sewage-contaminated water, especially in the course of swimming, and these theories have been revived from time to time with the demonstration of the poliomyelitis virus in sewage and other waste waters. While this possibility cannot be denied, it is extremely difficult to accept this as an important mode of spread. The theory would certainly not explain the general occurrence of the disease in the past, especially the large number and wide distribution of abortive cases, nor would it explain the wave-like character of spread. The spread of poliomyelitis in urban areas has not followed the water distribution system, on the contrary, with one exception,[2] there is no epidemic on record in which the pattern of spread was consistent with the hypothesis of transmission through sewage-polluted water.

The pollution of bathing beaches is a constant source of anxiety for community health specialists and it is customary for these recreational areas to be kept under constant surveillance. Nevertheless, convincing evidence to incriminate bathing in polluted water as a cause for outbreaks of intestinal disease is extremely hard to find. A few outbreaks of typhoid fever between 1920 and 1932 seemed ascribable to his mode of infection, but in extensive retrospective studies, only a few sporadic para-typhoid infections were attributable to bathing in natural bathing beaches.[3]

Only three epidemiologic studies[4] have been reported in this country which were designed to relate bacterial quality of natural bathing waters to human health. None of the three was conclusive or even highly suggestive as to suitable water quality standards for recreational waters. Eye, ear, nose, and throat ailments were the dominant illnesses reported. Gastrointestinal disturbances, the type that would be caused by fecal bacteria, accounted for 20% or less of the complaints. Swimmers showed distinctly higher rates of illness than non-swimmers, regardless of the bacterial quality of the water, a point which has been noted in other studies of illness experiences of swimmers.

A "new" disease has been reported as being acquired from swimming in fresh or brackish water. Amoebic meingoencephalitis, caused by a small free-living ameba, *Naegleria gruberi*, has epidemiologic features which suggest a waterbone origin. In fact, Butt[5] reported three fatal cases of primary amebic meingoencephalitis in which the evidence indicated that the disease was acquired during warm weather by swimming and diving in fresh water lakes or streams. Apley, et al[6] reported a case of meningitis in a child that may have been acquired by playing in a mud puddle. Callicott[7] and Duma[8] in separate papers have reported similar cases.

Retrospective studies of this infection and studies of environmental factors that influence the biology of ameba are underway and the results of these investigations should indicate the true scope of this disease and suggest methods of prevention and control. As Franklin Neva, M.D., asked in a recent editorial in the New England Journal of Medicine: "Is this another example of a new disease pattern that man has created by fouling his environment?"[9]

Unquestionably, recreational or occupational exposure to surface water increases the range of disease that can be acquired because of the accessibility of multiple portals of entry for micro-organisms, but gastrointestinal infections seem to play a small role, if the data thus far in the literature can serve as a reliable basis for this conclusion. However, infections of nasopharynx, mucus membranes, and skin abrasions would appear to be fairly common among persons frequently exposed to natural recreational waters.

There is, in fact, no significant epidemiologic basis for the total coliform standards used to assess the quality of bathing water. Commenting on the problem, E.R. Krumbiegel, M.D., Commissioner of Health for the City of Milwaukee, said, "The Milwaukee Health Department has applied standards for bathing water quality which are more tolerant of coliform organism concentrations than any standard I know of. Are the Milwaukee standards too lenient or are they more restrictive than is necessary?" The same fundamental question can be raised about standards for recreational water in the Potomac River Basin and other areas.

The simple answer is: we do not know. There is no evidence that human disease has been caused among persons swimming in water with a coliform in excess of 220, 500, or 10,000 ml. However, it has been noted that there is a sharp increase in the frequency of Salmonella when fecal coliform densities were above 200 organisms per 100 ml. In this connection, Geldreich[10] concluded that the inability to detect Salmonella in some instances of fecal pollution does not imply poor correlation of the fecal coliform test, but indicates the highly variable occurrence of Salmonella outbreaks.

Chemical Pollutants

Any review of water hygiene and community health must consider the major "new" water pollution problem which has emerged with the growth of the synthetic chemical industry. Wastes from this industry are reaching water courses in increasing numbers and amounts each year, both from the use of the manufactured products and from wastes produced during their manufacture. These chemicals reach the stream by way of municipal and industrial sewers, land drainage, or direct application of chemicals to the stream, lake, or impoundment.

Waste and products originating with the synthetic chemical industry are extremely complex in their composition and behavior. Many do not respond to modern water treatment procedures and they may therefore persist in streams for long periods of time. We do not have readily available techniques to detect most of these compounds in water, nor can they be removed from waste effluents. In fact, we know very little of the possible effects on community health at environmental levels. The urgency to evaluate these hazards is high on the list of community health priorities, but the difficulties are well-known and have been described in a comprehensive review by Stokinger and Woodward.[11]

Further light is focused on this problem by Dr. James Neel, Department of Human Genetics, University of Michigan.[12] He indicates that there seems to be very little danger of massive genetic damage from trace chemicals in water supplies, but it is highly possible that trace chemicals have increased human mutation rates. He further suggests that our ignorance of chemical mutagenesis in man or other mammals is such that it is impossible to find data to sustain even a brief argument.

Likewise, the role of carcinogenic substances and irritants is far from clean. The presence of such substances in a community water supply adds imponderably to the difficulty of setting a satisfactory water standard for such substances. Permitting no measureable quantity of carcinogenic agents in water would appear to be the only present means of dealing with such material, but it is scarcely a practical one.

Russell[13] has recently detailed the possible health effects of a sodium imbalance as an environmental pollutant in drinking water. Studying Santa Ana River, which serves as a principal water supply for Orange County, California, he found that 39.7% of the residents within that water district were supplied with water containing 110 milligrams or more of sodium per liter.

The county morbidity data for 1968 revealed that 54% of the deaths were caused by nine disease groups associated with high sodium retention. Data presented in that report, although incomplete, suggest the need for a more comprehensive study on the engineering, medical, and community health aspects of the sodium content of domestic water supplies.

Water mineralization and its influence on the course of coronary heart disease (CHD) and cardiovascular (CVD) has also been investigated by several workers during the past decade.

Morris, Crawford and Heady[14] described a highly negative correlation between water hardness and cardiovascular mortality in England and Wales. Linderman and Assenzo[15] explored the cardiovascular disease and soft-water correlation in Oklahoma and reported a positive but statistically insignificant correlation. Mulcahy[16] was able to show no correlation in similar studies conducted in the Republic of Ireland. From the Netherlands, Biersteker[17] reported a statistically negative correlation between water hardness and CVD in women but not in men. With the current trend toward artifically softened water, the work of Robertson[18] is of interest. He found that mortality from CVD significantly increased in the English town of Scunthorpe several years after the town started softening its municipal water supply.

Schroeder,[19,20] a long-time student of this problem, suggested that cadmium is perhaps the real factor and he reasons that corrosive soft water leaches cadmium from galvanized pipes and that this could readily enter a community's water supply. It has also been shown that cadmium in the kidneys can contribute to hypertension in some of the lower vertebrates and that a deficiency in chromium (trivalent state) favors arteriosclerotic disease. But here again is a large area in which the data are insufficient to clearly reject or accept the suggestions that there is a water quality factor influencing to any degree the development of certain cardiovascular disease.

As Wolman[21] recently concluded: "Although the disease evidence is elusive, some have been unable to resist the temptation to alarm the public by less than convincing data."

Water Quality Standards

The origin of current drinking water standards can be traced back to some 51 years ago when Congress passed a law which required the U.S. Surgeon General to establish interstate quarantine regulations. The first standards developed in 1914 included bacteriologic quality consistent with federal responsibility for communicable disease control. Since 1914, revisions (1925, 1942, and 1946) have covered inorganic chemicals, radioactivity, and in 1962, organic chemicals. It has been said that as testing procedures become more and more delicate, more ingredients will be added to the prohibited list; and several community health specialists have questioned whether this move toward zero risk is being considered realistically against resulting health benefits—or at what price.

It should be acknowledged that the present water quality standards are basically performance specifications; instead of providing the means by which standards can be met, they merely delineate goals. Since these standards are applicable to interstate carriers and disease control between states, only about 600 places in the United States are subject to federal inspections and regulations. Actually the revision of drinking water standards is now being considered within the federal establishment and will probably be brought to fruition as the new U.S. Environmental Protection Agency begins to devote more manpower and financial resources to this aspect of the water environment.

The American Water Works Association has already indicated its intention to work toward standards whose requirements can be translated more directly into measurements of water quality and which will be more refined as to specific contaminants.

Summary

Expanding industrial, agricultural and recreational activities have accentuated a built-in paradox where more and more water is needed but less becomes available at the required quality.

It is not only quality that has to be preserved and ameliorated but quantity. The fact that a certain level of quality can be assured in a technologically advanced era and the fact that proper quantities for the same community activities are reckoned with does not mean that the total water needs of an area have been satisfied. We must also be concerned about equality and this cannot be achieved until water in the proper quality and quantity is available to meet every segment of community need, industrial, domestic, and recreational.

While many of the waterborne disease pertubations have been laid to rest, physicians and other enlightened professional and lay groups have become increasingly concerned about viruses and the wide spectrum of chemicals now reaching the water contact cycle. At the present level of exposure, water pollutants do not seem to have a significant acute effect on community health with the exception of nitrates, which can cause methomoglobinemia and death in infants. Less well-defined, however, is the potential for chronic effects caused by long-term, low-level exposure.

Nevertheless, the call is loud and clear for a revision of drinking water standards whose requirement can be translated more directly into measurements of water quality which will be more refined as to specific contaminants.

Equally as loud is the plea for bacterial standards for bathing beaches, based on sound epidemiologic data. How soon these pleas will be heard and responded to is, today, a matter of conjecture.

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ECG DIAGNOSIS

(from page 497)

INTERPRETATION: 1. Second degree A-V block, Wenckeback type.

Several portions of this tracing, including the entire lower strip, suggest 2:1 A-V block of the Mobitz type. There are, however, some Wenckeback periods showing typical progressive prolongation of the PR interval until an atrial complex is completely blocked. This is demonstrated by the first three beats in the top strip, with a PR interval of 0.22 seconds in the first complex, 0.34 seconds in the second complex, then the third P wave occurs with no QRS following it. The next PR interval is approximately 0.23 seconds. Another such period appears at the end of the first strip, running onto the second strip with two more periods in the second strip. Observing these repeated cycles permits recognition of the 2:1 block in the bottom strip as a Wenckeback type with very short periods.

There is considerable evidence to suggest that the differentiation between Wenckeback and Mobitz type, second degree A-V block is important in the setting of acute myocardial infarction. The former may respond to Atropine, may be caused by digitalis, and appears to be less likely to progress to third degree A-V block than the Mobitz type.

Edited by
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Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (> 5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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Each white tablet contains: ethynodiol diacetate 1 mg./mestranol 0.1 mg.

Each pink tablet in Ovulen-28® is a placebo, containing no active ingredients.

Demulen® **Available in 21- and 28-pill schedules**

Each white tablet contains: ethynodiol diacetate 1 mg./ethinyl estradiol 50 mcg.

Each pink tablet in Demulen-28® is a placebo, containing no active ingredients.

Actions—Ovulen and Demulen act to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen and Demulen depress the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note—Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in the United States. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967. **2.** Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. 2:193-199 (April 27) 1968. **3.** Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. 2:651-657 (June 14) 1969. **4.** Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Amer. J. Epidem. *90*:365-380 (Nov.) 1969.

SEARLE
Products of **Searle & Co.**
San Juan, Puerto Rico 00936

Enovid-E® **Now available in the 21-pill schedule in refillable Compack® and three-cycle Triopak™**

Each tablet contains: norethynodrel 2.5 mg./mestranol 0.1 mg.

Actions—Enovid-E acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Enovid-E depresses the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Indication—Enovid-E is indicated for oral contraception.

The *Special Note, Contraindications, Warnings, Precautions* and *Adverse Reactions* listed above for Ovulen and Demulen are applicable to Enovid-E and should be observed when prescribing Enovid-E.

Enovid-E®

brand of norethynodrel with mestranol

SEARLE
Product of **Searle Laboratories**
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680
Where "The Pill" Began

CLEAR
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OBITUSSIN®
INE

The coughing season is here again. Time to rely on the four Robitussins and Cough Calmers to help clear the lower respiratory tract. All contain glyceryl guaiacolate, the efficient expectorant that works systemically to help increase the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions soothes the tracheobronchial mucosa, promotes ciliary action, and makes thick, inspissated mucus less viscid and easier to raise. Available on your prescription or recommendation.

For coughs of colds and "flu"

ROBITUSSIN®

Each 5 cc. contains:

Glyceryl guaiacolate	100 mg.
Alcohol, 3.5%	

For unproductive allergic coughs

ROBITUSSIN A-C® Ⓒ

Each 5 cc. contains:

Glyceryl guaiacolate	100 mg.
Codeine phosphate	10.0 mg.
(warning: may be habit forming)	
Alcohol, 3.5%	

Non-narcotic for 6-8 hr. cough control

ROBITUSSIN-DM®

Each 5 cc. contains:

Glyceryl guaiacolate	100 mg.
Dextromethorphan hydrobromide	15 mg.
Alcohol, 1.4%	

Robitussin-DM in solid form for "coughs on the go"

COUGH CALMERS®

Each Cough Calmer contains:

Glyceryl guaiacolate	50 mg.
Dextromethorphan hydrobromide	7.5 mg.

Relieves cough, clears sinuses and nasal passages—keeps them "drip-dry" but not bone dry

ROBITUSSIN-PE®

Each 5 cc. contains:

Glyceryl guaiacolate	100 mg.
Phenylephrine hydrochloride	10 mg.
Alcohol, 1.4%	

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	Expectorant-Demulcent	Cough Suppressant	Antihistamine	Long-Acting (6-8 hours)	Nasal, Sinus Decongestant	Non-Narcotic
BITUSSIN®	●					●
BITUSSIN A-C®	●	●	●			
BITUSSIN-DM®	●	●		●		●
BITUSSIN-PE®	●				●	●
UGH CALMERS®	■	■		■		■

this handy chart as a guide in selecting the formula that provides the benefits you want for your patient.

A·H·ROBINS

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Recommendations[†] on Combination Live Virus Vaccines

American Academy of Pediatrics

Committee on Infectious Diseases

In the September 15, 1971 *AAP Newsletter* sent to Academy members, the Committee on Infectious Diseases of the American Academy of Pediatrics stated its recommendations on the use of combination live virus vaccines. After a careful review of available data, the committee concluded that:

- "This information indicates that the products are both safe and effective when used as directed."
- The vaccine "...can, therefore, be recommended with the obvious advantages of reduction in the number of injections for any given child and a concomitant decrease in the required visits to a physician's office or clinic."

United States Public Health Service

Advisory Committee on Immunization Practices

In the April 24, 1971 issue of *Morbidity and Mortality Weekly Report,* the Advisory Committee on Immunization Practices of the United States Public Health Service presented recommendations on the use of combination live virus vaccines. The committee stated that:

- "Data indicate that antibody response to each component of these combination vaccines is comparable with antibody response to the individual vaccines given separately.
- "There is no evidence that adverse reactions to the combined products occur more frequently or are more severe than known reactions to the individual vaccines (see pertinent ACIP recommendations).
- "The obvious convenience of giving already selected antigens in combined form should encourage consideration of using these products when appropriate."

[†] For complete text of both recommendations see your MSD representative or write to Professional Service Dept., Merck Sharp & Dohme, West Point, Pa. 19486.

M-M-R*

(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE | MSD)

Single-dose vials

M-M-R, given in a single injection, fits easily into your routine immunization program for well babies.

Given at age 12 months, M-M-R provides for vaccination early in life against measles, mumps, and rubella.

MSD suggested immunization schedule for well babies

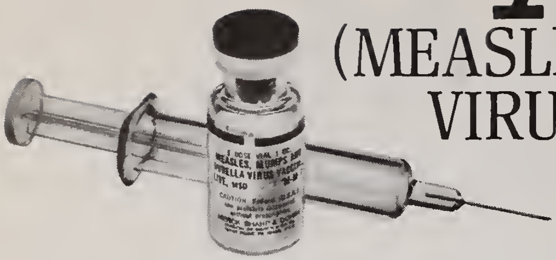
Age	Vaccine(s)
2 months	DPT (diphtheria-pertussis-tetanus) Oral poliomyelitis vaccine (triple)
3 months	DPT[1]
4 months	DPT Oral poliomyelitis vaccine (triple)
6 months	Oral poliomyelitis vaccine (triple)
12 MONTHS	**M-M-R (MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE, MSD)**

[1] This vaccination may be given at 3 months, 5 months, or at 6 months, depending on your preference or on the condition of the child.

Since vaccination with a live virus vaccine may depress the results of a tuberculin test for four weeks or longer, the test and the vaccine should not be given during the same office visit.

*Trademark of Merck & Co., Inc.

For a brief summary of prescribing information, please see following page.



M-M-R

(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE | MSD)

Single-dose vials

No untoward reactions peculiar to the combination vaccine (M-M-R) have been reported.

Moderate fever (101–102.9 F) occurs occasionally. High fever (over 103 F) occurs less commonly. On rare occasions, children who develop fever may exhibit febrile convulsions. Rash (usually minimal and without generalized distribution) may occur infrequently.

Since clinical experience with measles, mumps, and rubella virus vaccines given individually indicates that very rarely encephalitis and other nervous system reactions have occurred, such reactions may also occur with M-M-R. A cause and effect relationship, however, has not been established.

Excretion of the live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered the rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Must not be given to women who are pregnant or who might become pregnant within three months following vaccination.

Contraindications: Pregnancy or possibility of pregnancy within three months following vaccination; infants less than one year old; sensitivity to chicken or duck, chicken or duck eggs or feathers, or neomycin; any febrile respiratory illness or other active febrile infection; active untreated tuberculosis; therapy with ACTH, corticosteroids, irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; gamma globulin deficiency, i.e., agammaglobulinemia, hypogammaglobulinemia, and dysgammaglobulinemia.

Precautions: Administer subcutaneously; do not give intravenously. Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines; vaccination should be deferred for at least six weeks following blood transfusions or administration of more than 0.02 cc immune serum globulin (human) per pound of body weight, or human plasma.

Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur after vaccination.

Excretion of the live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered the rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Attenuated live virus measles and mumps vaccines, given separately, may temporarily depress tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be scheduled before vaccination, to avoid the possibility of a false negative response.

Before reconstitution, refrigerate vaccine at 2–8 C (35.6–46.4 F) and *protect from light*. Use only diluent supplied to reconstitute vaccine. If not used immediately, return reconstituted vaccine to refrigerator at 2–8 C (35.6–46.4 F), and discard after eight hours.

Adverse Reactions: Fever, rash; mild local reactions such as erythema, induration, tenderness, regional lymphadenopathy; parotitis; thrombocytopenia and purpura; allergic reactions such as urticaria; arthritis, arthralgia, and polyneuritis.

Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions.

Encephalitis and other nervous system reactions that have occurred very rarely with the individual vaccines may also occur with the combined vaccine.

Transient arthritis, arthralgia, and polyneuritis are features of natural rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Such reactions have been reported with live attenuated rubella virus vaccines. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after immunization should be considered as possibly vaccine related. Symptoms have generally been mild and of no more than three days' duration. The incidence in prepubertal children would appear to be less than 1% for reactions that would interfere with normal activity or necessitate medical attention.

How Supplied: Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the NIH Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin, with a disposable syringe containing diluent and fitted with a 25-gauge, ⅝" needle. Also in boxes of 10 single-dose vials nested in a pop-out tray with a separate box of 10 diluent-containing syringes.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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The Rx that says "Relax"

BUTISOL Sodium provides highly predictable sedative effect: minor dosage adjustments are usually all that's needed to produce the desired degree of sedation. (With 3 dosage forms and 4 strengths to make adjustments easy.)

BUTISOL Sodium offers prompt, smooth, relatively non-cumulative action: begins to work within 30 minutes...yet, because of its intermediate rate of metabolism, generally has neither a "roller-coaster" nor a "hangover" effect.

BUTISOL Sodium is remarkably well tolerated: a 30-year safety record assures you that there is little likelihood of unexpected reactions.

BUTISOL Sodium saves your patients money: costs less than half as much as most commonly prescribed sedative tranquilizers.*

These are four good reasons for prescribing BUTISOL Sodium for the many patients who need to have the pace set just a little slower. Its gentle daytime sedative action is often all that's needed to help the usually well-adjusted patient cope with temporary stress.

*Based on surveys of average daily prescription costs.

Butisol SODIUM®
(SODIUM BUTABARBITAL)

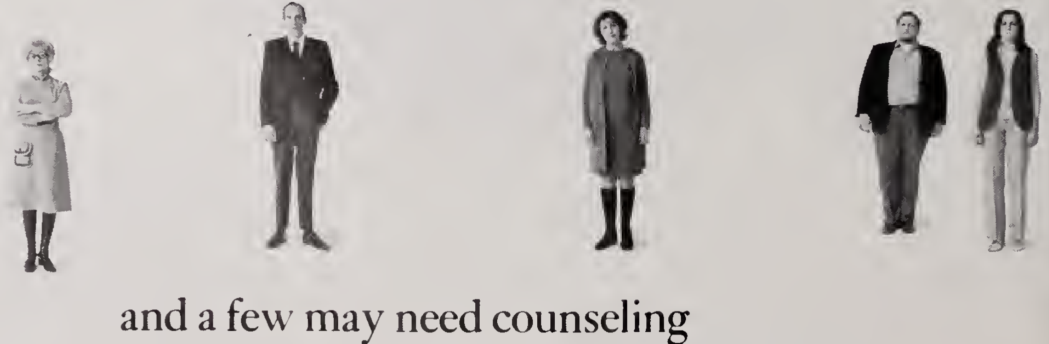
Contraindications: Porphyria, sensitivity to barbiturates, or susceptibility to dependence on sedative-hypnotics. **Warning:** May be habit forming. **Precautions:** Exercise caution in: moderate to severe hepatic disease; withdrawal in drug dependence or the taking of excessive doses over a long period, to avoid withdrawal symptoms; elderly or debilitated patients, to avoid possible marked excitement or depression; use with alcohol or other CNS depressants, because of combined effects. **Adverse Reactions:** Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and gastrointestinal disturbances are seldom seen. **Usual Adult Dosage:** For daytime sedation, 15 mg. to 30 mg. t.i.d. or q.i.d. For hypnosis, 50 mg. to 100 mg. **Available as:** Tablets, 15 mg., 30 mg., 50 mg., 100 mg.; Elixir, 30 mg. per 5 cc. (alcohol 7%). BUTICAPS® [Capsules BUTISOL SODIUM (sodium butabarbital)] 15 mg., 30 mg., 50 mg., 100 mg.

McNEIL McNeil Laboratories, Inc., Fort Washington, Pa. 19034

Everybody experiences psychic tension.

Most people can handle this tension.

Some people develop excessive psychic tension and need your counseling,



and a few may need counseling
and the psychotropic action of Valium® (diazepam).

Before deciding to make Valium
diazepam) part of your treatment
lan, check on whether or not the
atient is presently taking drugs
nd, if so, what his response has
een. Along with the medical and
ocial history, this information can
elp you determine initial dosage,
he possibility of side effects and
he ultimate prospects of success
r failure.

While Valium can be a most
elpful adjunct to your counseling,
t should be prescribed only as long
s excessive psychic tension per-
ists and should be discontinued
vhen you decide it has accom-
lished its therapeutic task. In
eneral, when dosage guidelines
re followed, Valium is well
olerated (see Dosage). For con-
enience it is available in 2-mg, 5-mg
nd 10-mg tablets.

Drowsiness, fatigue and ataxia
ave been the most commonly re-
ported side effects.

Until response is determined,
patients receiving Valium should
be cautioned against engaging in
hazardous occupations requiring
omplete mental alertness, such
s driving or operating machinery.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose® packages of 1000.

Valium®
(diazepam)

To help you manage excessive psychic tension

Healing nicely, but it still HURTS

HERE
Nasal fracture

EMPIRIN®
COMPOUND
c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

HERE Burns

When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures

Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

Ⓒ III **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

Wellcome

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Panalgesic
RELIEVES PAIN
CONTAINS: (BY WEIGHT)
OIL OF WINTERGREEN, ASPIRIN,
CAMPHOR AND MENTHOL 64.1%
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FOR EXTERNAL APPLICATION ONLY
CONTENTS UNDER PRESSURE · SEE CAUTION AND
USAGE
Apply where it hurts with gentle massage.
May be repeated as often as necessary
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Panalgesic©

RELIEVES PAIN

Usage: Apply where it hurts with gentle massage. May be repeated as often as necessary. A first aid in injuries, relieving pain and discouraging infection. Useful in industrial clinics—collegiate and professional athletic training programs.

**You may request a clinical supply.*

Dispensed in 4 oz. bottles, 6 oz. aerosol spray, pint and half gallon bottles.

WILLIAM P. POYTHRESS & COMPANY, INC. RICHMOND, VIRGINIA 23261

You don't have to walk to type.

Because being able to walk has nothing to do with being able to type. The only thing that matters is how well you can think and how fast your hands can move.

Remember, you're hiring her ability, not her handicap.

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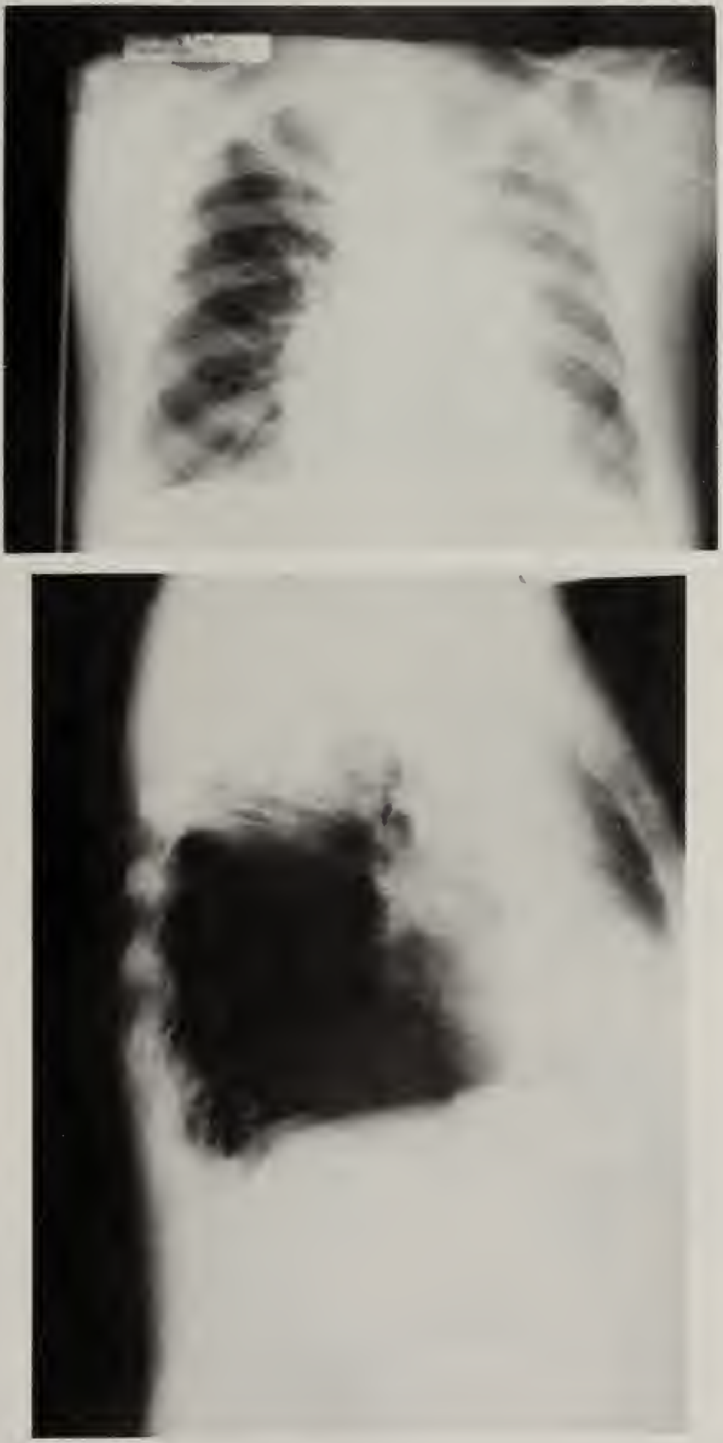
A DIVISION OF THE SCHOOL OF VISUAL ARTS SCHOLARSHIP FUND INCORPORATED

THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center

A 76 year old housewife presents with a nonproductive cough of several weeks duration. There were no other symptoms and the history was non-contributory.



(for diagnosis see page 520)

THE VIEW BOX

(from page 519)

DIAGNOSIS: Partial collapse of the left upper lobe (due to obstructing bronchogenic carcinoma)

The PA film shows a decrease in the volume of the left hemithorax. The left hemidiaphragm is slightly elevated and the ribs are closer together. The heart and mediastinal structures are minimally shifted towards the left. The upper (anterior) lobe is increased in density with obliteration of the left heart border (silhouette sign). The hilum is prominent. In the lateral projection a partially collapsed left upper lobe presents as a dense, wide band anterior-parallel to the sternum.

Bronchoscopy revealed an obstructing bronchogenic carcinoma at the origin of the upper lobe bronchus.

Edited by Gunther J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

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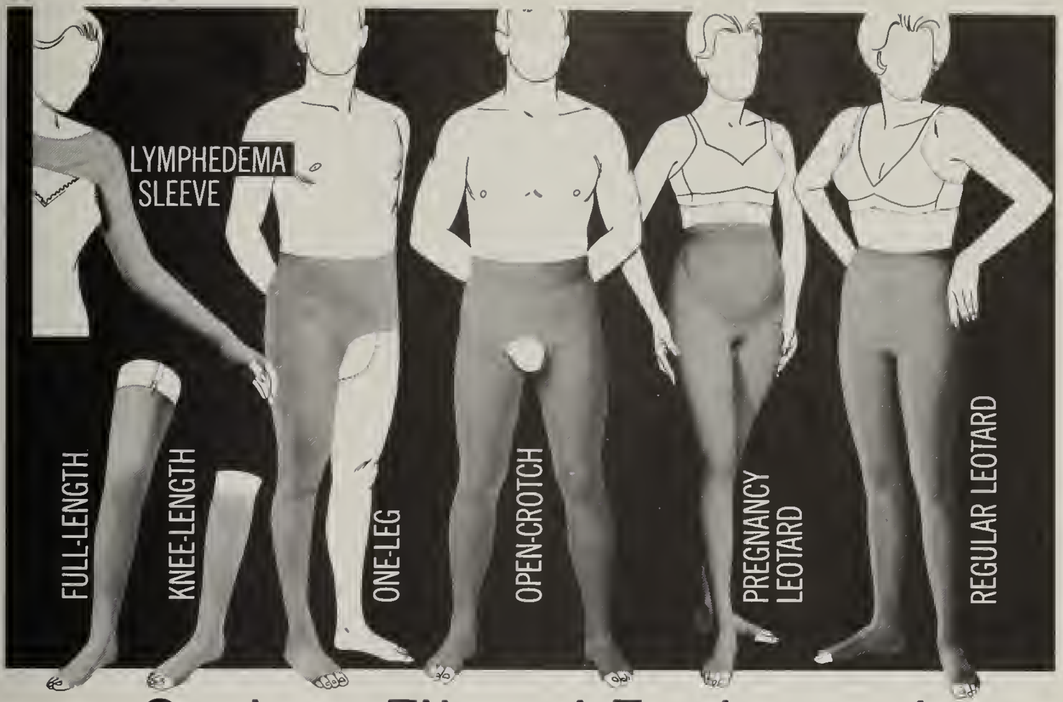
LYMPHEDEMA SLEEVE
FULL-LENGTH
KNEE-LENGTH
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REGULAR LEOTARD

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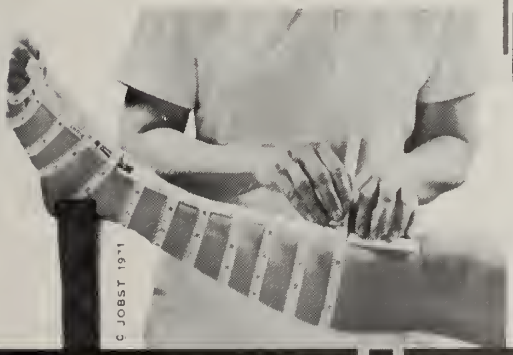

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Howard E. Ticktin Fund

A Memorial Lecture Fund has been created in memory of the late Howard E. Ticktin, M.D., who passed away April 2, 1973. The Howard E. Ticktin Fund has been established to provide a well known lecturer at the Annual Meeting of the George Washington University Alumni Association and, if funds are available, a visiting professorship at the George Washington University School of Medicine.

Dr. Ticktin was a 1954 graduate of the George Washington School of Medicine and a past president of the Alumni Association. Also, he had been a member of the George Washington University School of Medicine faculty since 1960. Dr. Ticktin was a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine and a member of the American Gastroenterological Association. He was a consultant to many institutions including the White House and the Food and Drug Administration.

Dr. Ticktin was a 14 year Active member of the Medical Society of the District of Columbia as well as chairman of the Society's Fee Committee for 1973.

Contributions totaling $10,000 to $15,000 are needed for the Howard E. Ticktin Memorial Lecture Fund. Contributions should be made payable to:

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> *"If we believe that men have any personal rights at all, then they must have an absolute moral right to such a measure of good health as society alone is able to give them."*
>
> Aristotle
>
> *"No one can really understand what it means to have cancer until they have it themselves."*
>
> Marguerite Piazza

At first reading, one would wonder how the two previous quotes relate. Consider first "what it means to have cancer"—and secondly, what does our medical society have to give to maintain good health for our fellow man. I hope the following article, and others to follow will nudge us all to using every available tool already at hand in the conquest of cancer.

This year approximately 47,000 people will die of cancer of the Colon-Rectum. Another estimated 79,000 new cases will be reported. In the District of Columbia in 1973 there will be 200 deaths from Colon-Rectal Cancer and 300 new cases—3 out of 4 of these patients can be saved—and you can do something about it!

Statistics are a bore. We have all studied them over and over again. Yet, for the purpose of this article a few must be repeated.

Routine health examinations with procto performed at the University of Michigan resulted in the discovery of single or multiple polyps in 46 of 477 examinations (9.6%) and one asymptomatic cancer (0.2%).

Gilbertsons series resulted in the finding of 20 carcinomas of the Colon-Rectum in 14,370 initial routine Procto examinations or one in 712.

Opinions have been expressed and reports published that the yield does not justify the time, effort, expenses, or morbidity risk incumbent with performing routine proctosigmoidoscopy on asymptomatic persons.

In April of 1970, a report of the Ad Hoc Colon-Rectal Cancer Study Committee of the Medical Society of the District of Columbia—based on the analysis of 613 patients, states that 37 asymptomatic patients were found to have cancer on a routine physical examination which included sigmoidoscopy. The report further states that "It is encouraging that considerable attention has been given to routine sigmoidoscopy on asymptomatic persons, as shown by the fact that 12.5% of patients were diagnosed in the pre-symptomatic stages of their disease," and "The importance of the routine rectal examination and sigmoidoscopy on asymptomatic patients as part of a yearly physical exam, especially on patients aged 40 and over, is evident."

There are those among us who do not follow the foregoing advice for a variety of reasons. (1) The yield does not justify the labor. (2) We refer patients to someone more practiced in the art. (3) The importance of this examination was not sufficiently impressed on us in medical school.

This brings us to the point of what the Cancer Committee of the Medical Society of the District of Columbia, the American Cancer Society, D.C. Division, Inc., and the practicing physician can do in a cooperative effort to reverse the rising morbidity and mortality rates from cancer of the colon and rectum.

The following is an interesting and enlightening quiz on Colon-Rectal cancer. We urge you all to take it. It will provide an opportunity to refresh your memory on the facts of this cancer "that nobody talks about."

Very shortly you will receive a questionnaire offering further opportunity for continuing education programs for Proctosigmoidoscopy to be scheduled at your individual convenience.

We need the help of every physician in promoting cancer control.

Robert S. Smith, M.D.
Chairman, Colon-Rectal Committee
District of Columbia Division
American Cancer Society

A Quiz On Cancer of the Colon and Rectum

There is considerable current interest in programmed instruction as a relatively new teaching technique. The following quiz on colon and rectal cancer was devised by Irving M. Bush, M.D., as a pretest to a course in programmed instruction being developed for use in the education of medical students and continuing education of physicians.

Because of widespread interest in colon and rectal cancer among physicians, it was thought that practicing physicians would find the quiz interesting. Correct answers are noted on page 528 of this issue.

Cancer Of The Colon and Rectum

Instruction: Each multiple choice question has one best answer which should be circled.

1. What is the rank of cancer of the colon and rectum among cancers causing death in the United States:
   (a) first
   (b) second
   (c) third
   (d) fourth or lower

2. Colorectal cancer ranks as a major problem mainly because of:
   (a) inadequate means of detection
   (b) underdeveloped surgical techniques
   (c) late diagnosis
   (d) poor prognosis even in early cases

3. An adequate digital rectal examination will detect approximately what percentage of all asymptomatic colonic and rectal cancers:
   (a) 15%
   (b) 35%
   (c) 50%
   (d) 75%

4. Full passage of a standard 25 cm. sigmoidoscope will uncover what percentage of additional cancers in asymptomatic patients:
   (a) 5%
   (b) 15%
   (c) 40%
   (d) 55%

5. In the modified Dukes' classification colorectal carcinoma, types B_1 and B_2 signify:
   (a) lymphatic involvement
   (b) muscle involvement
   (c) moderate tumor activity
   (d) rapid invasive growth

6. The five-year survival rate of patients with colorectal cancer which has extended through the muscularis propria of the bowel and at resection has not metastasized beyond the contiguous epicolic lymph nodes is:
   (a) 5%
   (b) 10%
   (c) 20%
   (d) 40%

7. The most unfavorable prognostic factor in carcinoma of the colon and rectum is:
   (a) tumor location in the transverse colon
   (b) occurrence at an early age
   (c) anemia below 10 grams
   (d) pencil-like stools

8. Tumors of the ascending colon in comparison to tumors of the descending colon are more likely to:
   (a) completely encircle the bowel
   (b) cause complete obstruction
   (c) be bulky and plaque like
   (d) spread earlier to the lymphatics

9. Some general symptoms of carcinoma of the colon and rectum are: blood in or on the stool, a palpable mass in the abdomen, change in bowel habits, and
   (a) dyspepsia, jaundice and unexplained weight loss
   (b) dehydration, unexplained weight loss and anemia
   (c) dyspepsia, unexplained weight loss and anemia
   (d) jaundice, dehydration, dyspepsia

10. Over the last few years, the role of polyps as precancerous lesions has been challenged. At present, a distinct single "polyp" of the colon when found on barium enema:
    (a) should be followed every six months with repeat barium enemas and stool guaiac determinations
    (b) should be biopsied and, if benign, other polyps, subsequently discovered, should be followed conservatively
    (c) should always be considered dangerous and removed for microscopic examination
    (d) should be ignored

11. The most common type of polyp of the colon and rectum is:
    (a) adenomatous polyp
    (b) papillary adenoma
    (c) villous adenoma
    (d) epithelioma

12. Papillary or villous adenomas:
    (a) have a low malignant potential
    (b) tend to recur after removal
    (c) are usually pedunculated
    (d) secrete small quantities of mucus

13. In the rectal ampulla, carcinomas are usually:
    (a) symptomatic quite early
    (b) always easy to palpate
    (c) metastasize first by vein invasion
    (d) spread primarily by way of the lymphatic system

14. A barium enema should be ordered:
    (a) when no tumor is found on annual proctosigmoidoscopic examination
    (b) when a single polyp is discovered on sigmoidoscopic examination
    (c) when the physician is unable to perform proctosigmoidoscopy due to inadequate bowel preparation
    (d) every three years in asymptomatic patients

15. Characteristic symptoms of carcinoma of the right colon are:
    (a) pain, obstruction and anemia
    (b) anemia, change in bowel habits and dehydration
    (c) pain, anemia and tumor mass
    (d) anemia, unexplained weight loss and blood in stool

16. Adenocarcinomas of the colon are usually:
    (a) bulky with rolled margins
    (b) not ulcerated
    (c) small and papillary
    (d) pebbled in appearance with poorly defined margins

17. Carcinoid tumors of the colon:
    (a) usually cause complete bowel obstruction
    (b) are characterized by rapid growth
    (c) metastasize early
    (d) occur in multiple locations

18. The most common symptoms of carcinoma of the left colon, in addition to blood in or on the stool and change in bowel habits, are:
    (a) decrease in the caliber of stools and obstruction
    (b) obstruction and a palpable mass
    (c) decrease in the caliber of stools and palpable mass
    (d) unexplained weight loss and anemia

19. In the physical examination of a patient with a suspect colorectal cancer, the most revealing phase of the examination is usually:
    (a) the abdominal palpation
    (b) the inspection of the anal area and digital rectal examination
    (c) observing the bowel mucosa upon insertion of the sigmoidoscope
    (d) observing the bowel mucosa during withdrawal of the sigmoidoscope

20. The most characteristic symptom of the far advanced stages of carcinoma of the rectum is:
    (a) pain
    (b) bleeding
    (c) tenesmus
    (d) mucus diarrhea
    (e) sensation of incomplete evacuation

21. The most common form of metastasis in cancer of the colon and rectum is by:
    - (a) venous transmission
    - (b) direct extension
    - (c) lymphatic involvement
    - (d) invasion by contiguity
    - (e) gravitational spread
    - (f) implantation

22. Three tumors that should always be considered whenever a lesion is discovered in the anal canal are:
    - (a) squamous cell cancer, malignant melanoma and basal cell carcinoma
    - (b) squamous cell cancer, basal cell carcinoma and lymphoganuloma venereum
    - (c) squamous cell cancer, malignant melanoma and carcinoid lesions
    - (d) squamous cell cancer, basal cell cancer and linitis plastica variant

23. In a patient with acute large bowel obstruction due to cancer of the colon, therapy should be directed towards:
    - (a) localization of the tumor
    - (b) decompression
    - (c) adequate surgical removal of the tumor
    - (d) identification of possible metastases

24. The most important aid in the future effective treatment of colorectal cancer would be:
    - (a) the development of more skilled proctologists and surgeons
    - (b) increased physician training in colorectal cancer recognition, pathology, classification and modes of spread
    - (c) the use of proctosigmoidoscopy as a part of the annual physical examination
    - (d) complete excision of every colorectal lesion

For an organization supposedly opposed to change, the AMA has made a lot of changes.

One of the most significant was the addition of an important new voice in the AMA—that of interns and residents. For the first time, these young physicians have not only a voice but also a vote in helping shape AMA policies.

Recently, the AMA House provided the same opportunities for membership and participation to medical students.

That's not all. In another important change, the AMA's council-committee structure has been streamlined. Some councils and committees have been dropped. Others have been made more efficient by reducing their size to seven members for councils and five for committees. And to permit more frequent infusion of new members and ideas, maximum tenure of service has been reduced to seven and five years, respectively.

The AMA *has* made a lot of changes. Changes to make it more responsive to the ideas of *all* physicians . . . changes to make it more effectively serve the needs of the profession.

Change will continue. But it will be decided only by those of you interested and dedicated enough to be a force in that change.

Join us.
We can do much more together.
American Medical Association
535 N. Dearborn St./Chicago, Ill. 60610

Correct answers to questions of quiz on cancer of the colon and rectum, pages 523 to 527.

1. a
2. c
3. a
4. d
5. b
6. c
7. b
8. c
9. c
10. c
11. a
12. b
13. d
14. b
15. c
16. a
17. d
18. a
19. d
20. a
21. c
22. a
23. b
24. c

book REVIEWS

Principles of Clinical Electrocardiography. M. J. GOLDMAN, M.D. Price, $8.00. Pp. 400. Los Altos, California: Lange Medical Publications, 1973.

The latest edition of this deservedly popular book is a continuation of excellence. The authors intention, as stated in his preface, is to present the basic concepts of electrocardiography and its clinical application, in simplified form. He succeeds admirably in accomplishing his intention. There are some relatively minor disappointments, according to the bias of this reviewer. This is a basic pattern recognition approach to the teaching of electrocardiography with certain ancient carry overs, if not hangups, of that method of teaching. For example, although the author states that the electrical axis is not synonymous with the anatomic position of the heart and that there is not a high degree of correlation between these two phenomena, he goes on to devote fifteen pages to the effect of heart position on the electrocardiogram. Particularly irritating to this reviewer is the continuation of the concept of clockwise and counter clockwise rotation to describe the location of the transition zone of the precordial complexes. Apart from the over simplification and inaccuracy of the concept, the terms introduce confusion vis-a-vis the use of the same terms to describe rotation of the QRS loop in the vectorcardiogram. Otherwise, however, there is repeated use of vector concepts in explaining the patterns of the normal and abnormal electrocardiograms. Thus, a brief vector analysis supplements and complements the pattern descriptions. The eighth edition introduces the subject of bundle of his recordings, which makes it a modern text. However, there is disappointingly little use made of the technique in discussing certain areas where its application would be of practical help in interpretating the electrocardiogram. However, the introduction to the technique, with its terminology is a welcome addition.

The easy to read and to-the-point prose, the generous use of excellent diagrams, the interspersion of clear electrocardiographic recordings breaking up the text, are a continuation of the features that have made previous editions so popular. There is a very simple and understandable, well illustrated introduction to spatial vectorcardiography. There is a nice collection of miscellaneous abnormal electrocardiographic patterns. There is the appendix which neatly summarizes the interpretation of abnormalities of the electrocardiogram, according to the individual components of the PQRST complex, as well as the arrhythmias. There are some useful simple tables in the back. The index is good.

In summary, this book is an effective teacher of electrocardiography, most useful for medical students, nurses as well as physician beginners and novices in electrocardiography. It is not meant to be a sophisticated reference. However, the teacher of electrocardiography can learn some useful techniques and approaches from this book. The soft cover keeps the price down, and makes this one of the great medical book bargains of these inflationary times.

GERALD I. SHUGOLL, M.D.

Review of Physiological Chemistry. H. A. HARPER. Price, $8.50. Pp. 545 with illustrations. Philadelphia, Pennsylvania: W. B. Saunders Company, 1973.

A book by this title is expected to supply a condensed source of information that is otherwise presented in much more detail in standard textbooks. It should permit the reader to prepare himself for examinations of state and specialty boards if once upon a time he had studied the subject. And it should allow a teacher to hand a student an outline which is equally as "good" or "better" than one the teacher might have prepared himself. Harper's "Review" fills these requirements well.

Beginning in 1939, this book was copyrighted again five years later, then seven years later and thereafter every two years. Such a record does not only attest to the popularity of this volume—it also reflects the author's desire to bring it up to date. Thus it is gratifying to note that such a recent development as affinity column chromatography is mentioned while such an overplayed concept as Donnan Equilibrium has been relegated to an appendix section.

No further words of praise are needed.

FELIX FRIEDBERG, Ph.D.

Cardiac Hypertrophy. NORMAN H. ALPERT, *Editor.* Price, $25.00. Pp. 641 with illustrations. New York: Academic Press, 1971.

This monograph is concerned with the many aspects involved in understanding cardiac hypertrophy. It is not an esoteric treatise of interest to only a few scientists. Rather, it is a prodigious and profound presentation that clarifies and distinguishes cardiac growth from enlargement of other organs. Cardiac Hypertrophy provides a forum for the research scientist and physician.

Original investigations, by 87 contributors renowned in the field, reveal the myriad phenomena involved in Cardiac Hypertrophy. Current concepts and recent advances comprise forty-eight chapters. Diverse disciplines of science expound the thesis that Cardiac Hypertrophy is the heart's expression of and to an adaptive mechanism of increased work-load.

Initial chapters focus, teleologically, on the unique character of the heart. At birth the number of muscle fibers is equal in both ventricles. However, with the first natal breath and consequent closure of the ductus arteriosus, disparity in ventricular size is manifest due to altered ventricular function and responsibility. Thus, inequality of ventricular muscle mass is not predetermined genetically. Ventricular hypertrophy is achieved not by cellular hyperplasia but through the increased number of intra-cellular organelles. Sarcomere length is not changed; constituent myofibrils increase only through an increase of myofilaments. Myosin, mitochondria, sarcoplasmic reticulum resort to molecular turnover to renew intra-cellular integrity and function.

Cardiac growth cannot continue unrestricted. It is influenced by many factors: protein metabolism and turnover of RNA and DNA, blood supply and hormonal milieu. Increase in DNA in the mature animal may be due to a proliferation of interstitial cells and other non-muscular and non-contractile elements, hence, an unreliable index of myocardial cell hypertrophy.

To physician and scientist, alike, the interface where normal cardiac growth becomes abnormal ventricular hypertrophy, is often indiscernible. Mechanical and energy characteristics may seem unchanged. However, whether as an isolated muscle strip or as a total functioning unit scrutinized in the physiological or chemical laboratory, both animal and human myocardium reflect altered correlates of energetics and mechanical efficiency. Sub-clinical and overt evidence of heightened end-diastolic ventricular pressure and volume and decreased ventricular ejection fraction represent sustained effects of increased work loads. Reluctance to accept the conclusions of the experimental laboratory, where these correlates are artificially and acutely induced is suspected may be regarded as invalid comparisons to myocardial hypertrophy in man. Likewise, clinically, the border between the normal and the abnormal myocardium is subtle, often difficult to recognize and even defies detection by the most sensitive non-invasive techniques. Nevertheless, physiologic observations in the cardiac laboratory support the concept that ventricular hypertrophy in man, as well as in the animal, is an adaptive mechanism and the consequence of increased cardiac work.

Finally, the electrical correlates of the hypertrophied heart are presented in the concluding chapters. An introduction to "advanced" electrocardiography, the electrical field surrounding the hypertrophied right ventricle, body surface potentials, di-pole and multi-pole approach to electrocardiography, reflect the variegated disciplines and modalities that were mobilized to extract the maximum information and clearest possible understanding of the biologic dynamics of ventricular hypertrophy.

In any multi-authored text, repetition is unavoidable. It does serve to reemphasize current concepts. Here and there, an occasional chapter is all too brief and seems a mere editorial and not worthy of inclusion between its excellent chapters.

In this monograph, Editor Platt and his prestigious participants provide the physician and investigator with an abundant volume of information. "Cardiac Hypertrophy" deserves a place on the shelf of every medical library.

BENJAMIN MANCHESTER, M.D.

Tissue Typing Techniques. HEATHER M. DICK AND W. BARRY CRICHTON. Price, $13.75. Pp. 152. Baltimore, Maryland: The Williams & Wilkins Company, 1972.

HL-A typing techniques would have been a better title for this well written text. The authors suggest a more specific title, "the broad term 'tissue typing' is often loosely applied to the recognition of individual HL-A antigens, but lymphocyte or platelet typing would often be a more accurate definition." Although the practice of organ transplantation has reached the level of public knowledge typified by television medical dramas, most practicing physicians do not need the specific, how-to-do-it information this book contains.

The authors do describe in clear, easily understood fashion the typing techniques used in their department at the Glascow Royal Infirmary. All aspects of the subject are discussed: antigen preparation and storage, the variety of antigen tests available, the problems of uniformity of typing sera and nomenclature, etc. Each section includes a brief discussion of the historical experiences which led to present day practice. This lifts the book above the run-of-the-mill cookbook for clinical laboratory texts. The introductory chapter is particularly useful for describing the evolution to the current state of this art.

Producing and standardizing HL-A antisera presents so many problems that tissue typing remains a discipline to be practiced by only a few laboratories. This book consequently is of real interest only to workers in the field. For them it can be used as a methods book or a check on their own techniques and supplies.

PHILLIP PERIMAN, M.D.

American Cancer Society

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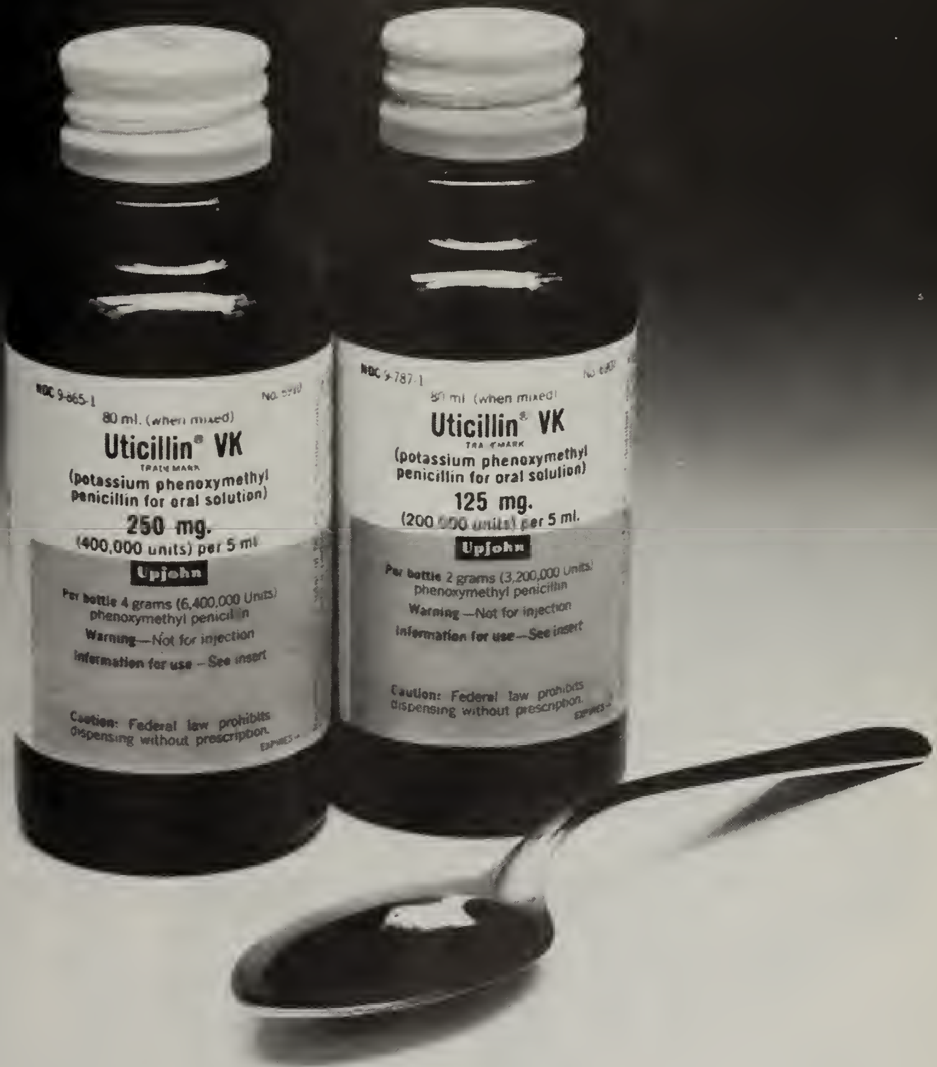
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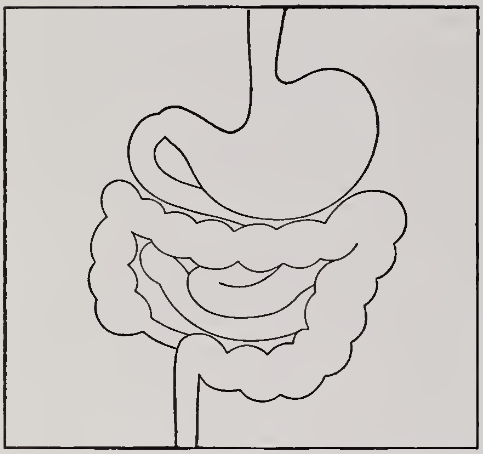

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obituaries

Jerome H. Epstein, M.D.
1925–1973

Dr. Jerome H. Epstein, specialist in gastroenterology, died August 4, 1973. He resided at 8528 West Howell Road, Bethesda, Maryland.

Born in Jersey City, New Jersey, he received his A.B. degree from New York University; his A.M. degree in biochemistry from George Washington University; and his medical degree from George Washington University. He interned at George Washington University Hospital and served residencies at D.C. General Hospital and George Washington University Hospital.

He was on the staffs of George Washington University Hospital, Sibley Memorial Hospital, Washington Hospital Center, Georgetown University Hospital and Doctors Hospital.

From 1944-1946, he served in the U.S. Navy in the Philippine Sea Frontier; in 1950 he was employed as a Junior Assistant Sanitarian, U.S. Public Health Service at the National Institute of Health.

He was a clinical instructor in medicine at George Washington University and the author of numerous scientific papers.

Dr. Epstein was an Active member of the Medical Society of the District of Columbia. In addition, he was a member of the American Federation for Clinical Research and the Society for Experimental Biology and Medicine.

He is survived by his wife, Madeline, of the home address; sons, Todd and Jonathan; and a daughter, Jody.

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CARE – New York, N.Y. 10016

Ella M. A. Enlows, M.D.
1889–1973

Dr. Ella M. A. Enlows, a practicing physician in the Washington area for many years who specialized in diseases of the ear, nose, and throat, died June 25, 1973. She resided at 516 East Ridge Valley Drive, Miami, Florida.

Born in St. George, West Virginia, she received her A.B., M.S. and Ph.D. degrees from George Washington University and her medical degree from Johns Hopkins Medical School. In addition, she completed one year of graduate work in Otolaryngology at the University of Pennsylvania.

She served her internship at Garfield Hospital and was on the hospital staffs of Episcopal E.E.N.&T. Hospital and Children's Hospital in Washington and on the courtesy staffs (with surgical privileges) of George Washington, Garfield, Children's, Doctors, Suburban and Sibley Memorial Hospital.

During her long career, Dr. Enlows was a scientific assistant and assistant pathologist for the U.S. Dept. of Agriculture, a bacteriologist for the U.S. Public Health Service, and an assistant in chemistry at George Washington University. She contributed numerous articles to scientific publications.

In addition to being a Life member and past second vp of the Medical Society of the District of Columbia, Dr. Enlows was a member of the American Medical Association, the Johns Hopkins Surgical Association, the American Academy of Ophthalmology and Otolaryngology and past president of the American Medical Womens Association.

Dr. Enlows was the wife of the late Harold F. Enlows, who for 25 years was the national director of the Red Cross safety program.

She is survived by her sister Violet K. Austin of Miami, Florida.

Information to Authors of Manuscripts Submitted to The Medical Annals of the District of Columbia

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The entire manuscript, including footnotes and case reports, should be submitted unrolled, with double type spacing. An original copy and one carbon copy should be submitted, and a carbon copy should be retained by the author.

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The by-line, the author's given name and initial or given name alone should be supplied. The M.D. degree or highest academic degree should be listed for each author. Not more than six names should be included as authors, unless the communication is the report of a committee.

The footnotes, hospital and university affiliation when study was done, should be listed. Present affiliation and location (if different from that at time of study) should be given. Acknowledgements should be limited to persons, foundations, agencies or companies supplying drugs, funds or apparatus free of charge or otherwise making an extensive contribution to the study.

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References should be double spaced, on a separate sheet, and listed in order of citation in the text. Superior numbers should be inserted in the text at points of citation.

References should be given in the style regularly used in THE ANNALS, eg:

> Seremetis, M.D., DeGuzman, V.C., Lyons, W.S., Peabody, J.W.: Complications of Cardiac Pacemakers, Medical Annals of D.C., 1973, 42, 165.

TEXT

Use generic or descriptive names of drugs when available. Trade names, capitalized, may be given in parentheses when the drug is first mentioned.

Statistics should be checked for consistency within the text and for agreement with graphs or tables.

Laboratory data should not be given in abbreviated form but in full (e.g., "hemoglobin level, 12 Gm. per 100 ml." rather than "Hb. 12 GM.%).

Figures should be used for number 10 and above, laboratory measurements, percentages, and ages.

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Centigrade equivalents should be given for Fahrenheit body temperatures, and vice versa.

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There should be no discrepancies in the totals.

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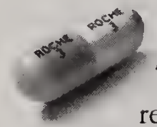

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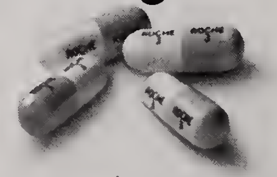

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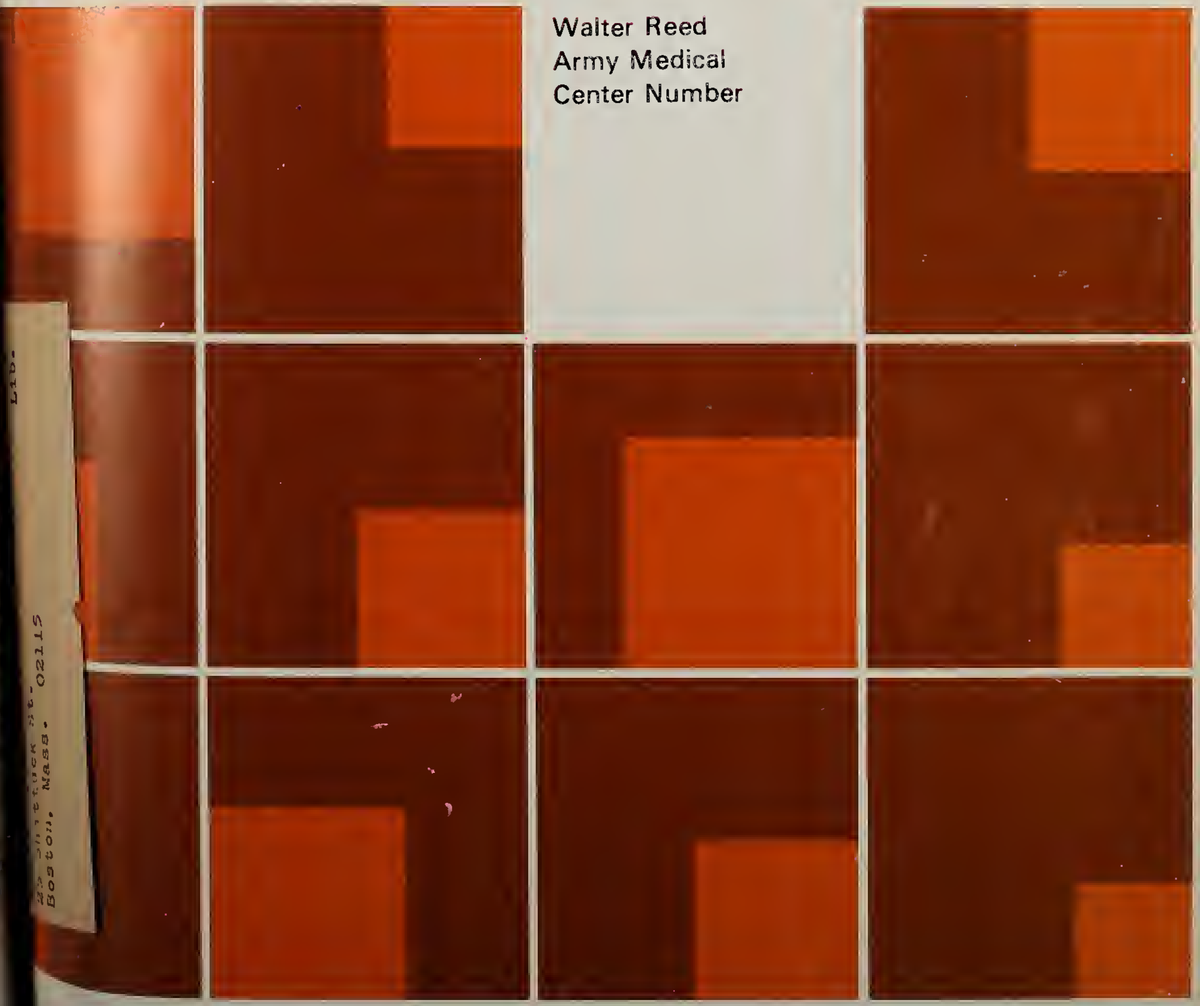

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President's Message
An Indignity. Irving Burka, M.D. . . . 1

Editorial
Walter Reed Army Medical Center. Robert Bernstein, M.D. . . . 3

SCIENTIFIC ARTICLES

Hyperfunctioning Thyroid Nodules that Become "Cold". Kenneth D. Burman, M.D., CPT, MC, Raphael L. Warkel, M.D., MAJ, MC and Leonard Wartofsky, M.D., LTC, MC . . . 541

Adrenal Insufficiency Resulting from Metastasis of Non-Functioning Adrenocortical Carcinoma. Hunter Heath III, M.D. and Patrick R. Bergevin, M.D. . . . 545

Metastases in Bone Marrow and Pancytopenia from Carcinoma of the Lung. Maj. Ivan P. Law, M.D., MC, U.S.A.R. . . . 548

Dysphagia Lusoria: A Forgotten Entity? Richard C. Cammerer, M.D., MAJ, MC . . . 553

^{99}Tc Sodium Pertechnetate Scanning of the Abdomen. A Valuable Tool for Detection of Meckel's Diverticulum. Reynaldo G. Geerken, M.D., MAJ, MC and Daniel B. Collin, M.D., MAJ, MC . . . 556

Cardiorespiratory Complications of Intravenous Drug Abuse. Ronald R. Blanck, MAJ, MC, Peter T. Singleton, M.D. and Jules L. Bedynek, COL, MC . . . 559

Ineffective Erythropoiesis. Robert P. Brouillard, M.D., MAJ, MC . . . 563

SPECIAL ARTICLE

New Concepts in Asthma. Hyman M. Kaplan, M.D. and George W. Ward, Jr., M.D. . . . 566

OTHER FEATURES

ECG Problems . . . 558

The View Box . . . 552

(continued)

Committee Report 579

Adolescence and Preadolescence Appropriate Attitudes & Values

New Members 581

Book Reviews 583
Progress in Liver Diseases. (Popper and Schaffner) Reviewed by Allen L. Ginsberg, M.D.

Hemodialysis. (Bailey) Reviewed by Anne M. Thompson, M.D.

Physiology, Emotion and Psychosomatic Illness. (Ciba Foundation Symposium) Reviewed by Morris Kleinerman, M.D.

Photomicrography. (Lawson) Reviewed by Chandler Smith, M.D.

The Management of Neonates and Infants with Congenital Heart Disease. (Billig and Kreidberg) Reviewed by Antonio C. de Leon, Jr., M.D.

Auxiliaries in Health Care. (Fendall) Reviewed by Martin S. Wolfe, M.D.

Vectorcardiography. (Benchimol) Reviewed by Keith M. Lindgren, M.D.

Obituaries 587

Herbert H. Schoenfeld, M.D.
Frederick O. Coe, M.D.

Information for Authors 591

Advertising and Subscription Information 594

Index to Advertisers 594

Medical Society of D.C.
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President's Message

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An Indignity

IRVING BURKA, M.D.

The Department of Health, Education and Welfare recently proposed new anti-fraud rules regarding Medicaid. Patients under Medicaid will be asked to tell the Government whether their doctors are really providing the services for which they are billing.

Under this new rule, those states with computerized management systems would be required to notify Medicaid recipients of specific services rendered by doctors and dentists, for which the bills were submitted. It would also require these state agencies to inform patients of the new criminal penalties for fraud which Congress approved last year.

Shades of Nazi Germany! Control and regimentation generates fear, sets one class against another, and pits consumer against provider and patient against physician. Control by fear . . . (or "if you don't watch out, the big cruel doctor will get you!") This, then, is the Government's way of providing better quality health care for our population who need it most.

This type of action is an insult to the dignity of our profession. It can only lead to resentment and militancy.

For the past several years, we in the Profession, along with the State Medicaid agencies, have stressed the absolute need for the private sector of medicine to become involved in the care of Medicaid recipients. We have stressed and re-stressed that what is most needed is quality care, in an environment that is away from the "brown bench" syndrome and into the stream of American middle class where one is not just a number, but an entity unto himself. Therefore, an environment involving a direct relationship between doctor and patient. This, in my opinion, is Medicine at its best, and for which we should all strive.

To provide decent, meaningful, quality health care for all of our people requires an intelligent, coordinated effort on the part of Government, the public, doctors, and other health providers. United, in concert, we can achieve these goals without the planting of suspicions, fears and mistrusts among us.

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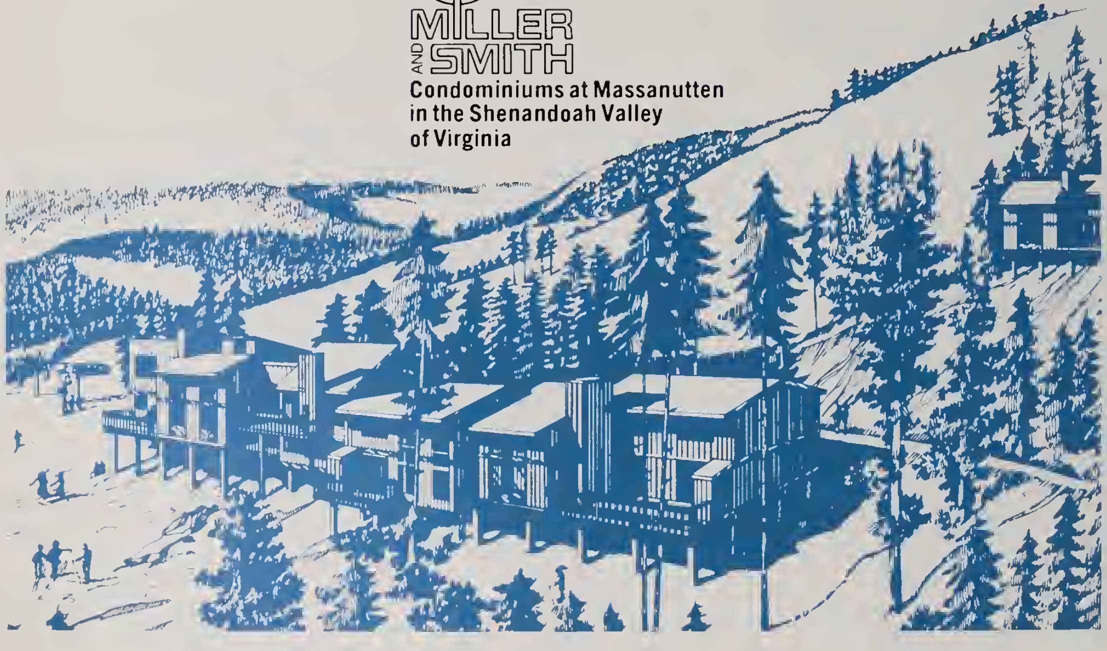

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The Center's second component, the Army Medical Department Professional Service School was formed by combining the Army Medical School with the Army Veterinary School and the Army Nursing and Dental Schools. These components and the Hospital united under one command, officially became the Army Medical Center on September 1, 1923.

The American public, however, impressed by the national reputation of the Walter Reed General Hospital, continued to refer to the entire installation simply as "Walter Reed." For this reason, and to pay further tribute to the conqueror of yellow fever, the installation was renamed "Walter Reed Army Medical Center" on the 100th anniversary of the famed doctor's birthday in September 1951.

Other installations which have joined the Center in the fight against disease over the years include the Walter Reed Army Institute of Research, The Armed Forces Institute of Pathology, The U. S. Army Audiology and Speech Center, the Walter Reed Army Institute of Nursing, The U. S. Army Institute of Dental Research, The U. S. Army Regional Dental Activity and several other smaller units. To these the Center offers administrative and logistical support.

In additon to the Hospital, major research is pursued at the Walter Reed Army Institute of Research, The Armed Forces Institute of Pathology and at the U. S. Army Institute of Dental Research.

Among the many outstanding contributions these research efforts have produced are the chlorination of water, the isolation of the Rubella measles virus (1965), the development of a typhoid vaccine by Colonel Joseph F. Siler.

Research programs have led to the development of vaccine which virtually wiped out the incidence of equine encephalomyelitis in the USA. Through long and arduous investigations the epidemic hemorrhagic mortality rate was reduced from 16 percent to 2 percent, with a 50 percent reduction in incidence of the disease. These are but a few of the breakthroughs resulting from the investigative work of Reed's medical researchers.

Although emphasis is placed on military-medical problems, results of studies here are shared with the civilian population of the nation.

Walter Reed Army Medical Center is a self-contained community. Its daily population of 8,000 patients, officers, enlisted personnel and civilian employees is served by many service facilities both at the Main Section and at Forest Glen. The civilian workforce comprises approximately fifty percent of the total manpower figure. Fifty-two percent of all personnel at the Center are minority employees.

Visitors are impressed by Walter Reed's grounds and pink-brick Georgian architecture set in the midst of tailored lawns, winding roads and colorful gardens. Only during the past year has the campus-like atmosphere been disturbed by the vast demolition and construction underway to prepare the site of the new hospital. Relandscaping continues as the construction goes on.

In its more than six decades of service, the Hospital has treated a vast number of patients. In addition to its more than 16,000 admissions annually, Walter Reed Army Medical Center operated one of the most sophisticated outpatient services in the Army with an annual patient load exceeding 600,000.

EDITORIAL

Dedicated to serve the American soldier and his family, the Walter Reed Army Medical Center provides for them the best medical treatment in the world. It is a fine example in the concept of people making medicine work for people.

Walter Reed Army Medical Center maintains training programs to satisfy not only the training needs of the military, but also through affiliations assists the needs of civilian institutions in and out of the Washington area; to include Georgetown University, George Washington University, Howard University, Catholic University and the University of Maryland. Walter Reed conducts training programs primarily to satisfy the professional personnel demands of the Army; however, the vast majority of all the residents, nurses, corpsman, hospital administrators, technicians, etc, eventually leave the service and enter civilian life thus WRAMC becomes a training source for medical personnel for thousands of needy civilian communities. One example of these training programs is the graduate medical education program with thirty-one interns, two hundred twenty-five residents and fellows in thirty-six separate specialty training programs.

Via its affiliations, Walter Reed participated in in-house training of three hundred forty-three students from the medical and allied medical educational programs of our affiliated institutions during fiscal year 1973.

In addition to their teaching responsibilities at WRAMC, many of the medical staff hold non paying professorships at local medical schools and assist in all phases of teaching.

These far reaching affects have caused Walter Reed to be described by the Army Chief of Staff as not belonging to the Medical Department, not the Army, but rather to the Nation.

ROBERT BERNSTEIN, M.D.
Major General
Commanding

Our Appreciation to

ROBERT A. HOLMES, M.D.
LTC MC

Chief, General Medicine Service

for coordinating this

Walter Reed Army Medical Center Issue.

acute arthritic inflammation...heat that freezes

In acute rheumatoid arthritis consider Tandearil. The anti-inflammatory action of Tandearil quickly helps reduce heat, pain, swelling, and stiffness. Results are usually seen in 3 or 4 days. Try it for a week when the symptoms defy aspirin control.

Remember that Tandearil is not a simple analgesic. It should not be used on patients responding to routine therapy. Before using, please read the prescribing information. It's summarized below.

Tandearil® helps take the heat off

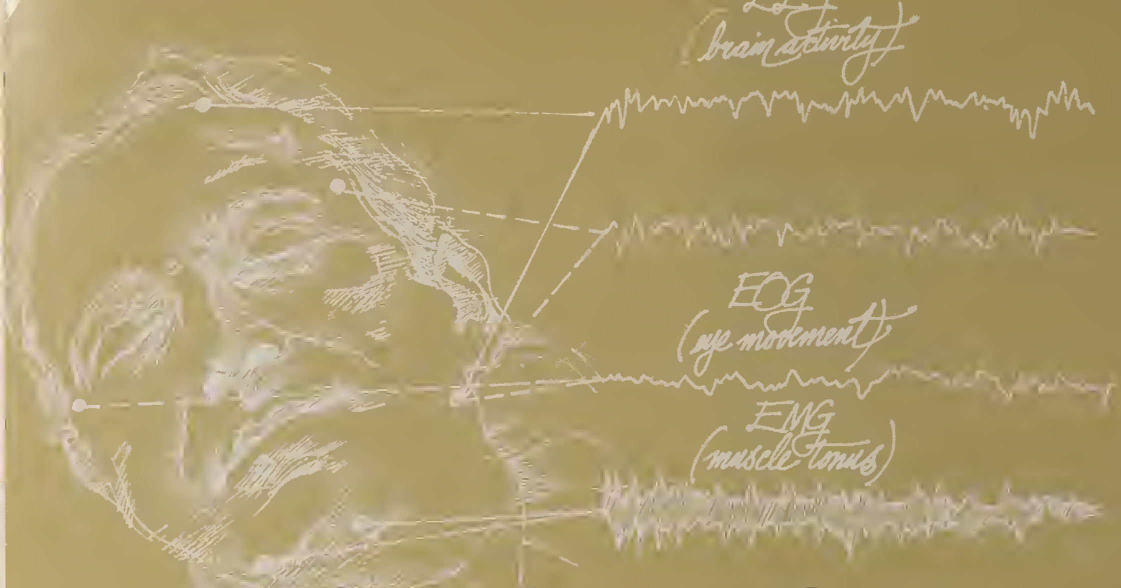
oxyphenbutazone NF

Geigy

Tablets of 100 mg.
Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Acute gouty arthritis, rheumatoid arthritis, rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existence of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
(B)98-146-800-F (10/71)
For complete details, including dosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

TA 9041



More than sleep..

your choice of sleep medication is wisely based on more than sleep-inducing potential

sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dalma (flurazepam HCl); no depression of cardiac or respiratory functi was noted in patients administered recommended or higher dos for as long as 90 consecutive nights.

In most instances when adverse reactions were reported, they were mild, infrequent and seldom quired discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. Diz ness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

sleep for 7 to 8 hour without need to repeat dosage

No sleep me cation has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia patie given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer nig time awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to repe dosage during the night.

eep with onsistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration, with no need to increase dosage.

Dalmane (flurazepam HCl) is a distinctive sleep medication—a
odiazepine specifically indicated for insomnia. It is not a bar-
rate or methaqualone, nor is it related chemically to any other
lable hypnotic.

When your evaluation of insomnia indicates the need for a sleep
lication, consider Dalmane—a single entity nonnarcotic, non-
iturate agent proved effective and relatively safe for relief of
mnia.

DALMANE®

(flurazepam HCl)

When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients)
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening in patients with recurring insomnia or poor sleeping habits and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, e.g., excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE

ROCHE LABORATORIES
Div., Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

The Weight of Professional Opinion

It's time for action to defend the laws and regulations that protect your patients against drug substitution.

These professional and trade organizations are united in supporting antisubstitution statutes and regulations:

The American Academy of Dermatology

The Board of Directors of the American Academy of Family Physicians

The Executive Board of the American Academy of Neurology

The Committee on Drugs of the American Academy of Pediatrics

The American College of Allergists

The Executive Committee of the American College of Obstetricians and Gynecologists

The Board of Regents of the American College of Physicians

The Board of Trustees of the American Dental Association

The Board of Trustees of the American Medical Association

The American Psychiatric Association

The Executive Committee of the National Association of Retail Druggists

The Board of Directors of the Pharmaceutical Manufacturers Association

The National Wholesale Druggists' Association

Jint Statement on Antisubstitution Laws and Regulations

The purpose of this statement is
affirm the support of the participat-
g organizations for the laws, regula-
ns and professional traditions which
ohibit the unauthorized substitution
drug products.

Traditionally, physicians, den-
ts and pharmacists have worked
operatively to serve the best inter-
ts of patients. Productive coopera-
n has been achieved through
utual respect as well as a common
ncern for the ideals of public
rvice. This mutual respect has been
flected, in part, by joint support
er the years for the adoption and
forcement of laws and regulations
ecifically prohibiting unauthorized
bstitution and encouraging joint
scussion and selection of the
urce of supply of drug products.
e basic principles of medical, den-
l and pharmacy practice are thus
ilized and preserved in the interest
patient welfare.

The antisubstitution laws have
t obstructed enhancement of the
ofessional status of pharmacy any
ore than they have in and of them-
lves guaranteed absolute protec-
n from unsafe drugs, or freed
ysicians, dentists and pharmacists
om their responsibilities to patients.
a practical matter, however, such
ws and regulations encourage inter-
ofessional communications regard-
g drug product selection and assure
ch profession the opportunity to
ercise fully its expertise in drug
age, to the advantage of patients.

Physicians and dentists should
e urged to increase the frequency
d regularity of their contacts with
armacists in selection of quality
ug products, recognizing that economies to patients can be improved through such communication, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physicians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selection remain primary and do not permit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved understanding and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthorized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

Add your opinion to the weight of other professionals and send it to your state assemblyman or legislator.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D. C. 20005

ROCHE announces new BACTRIM™

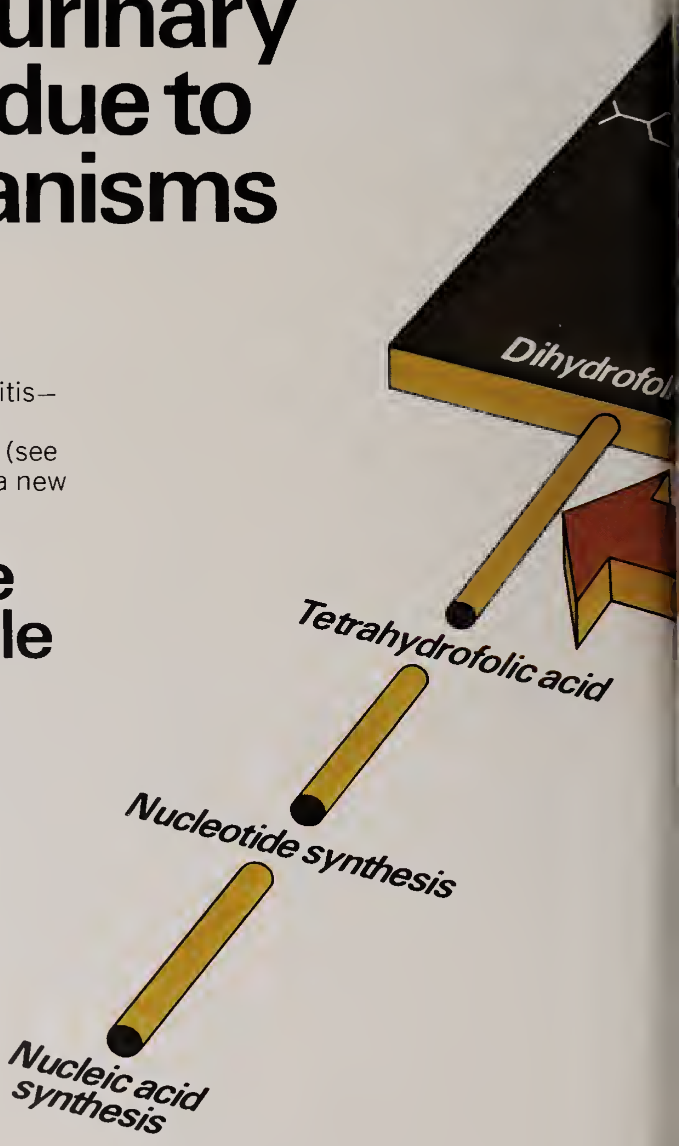
Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

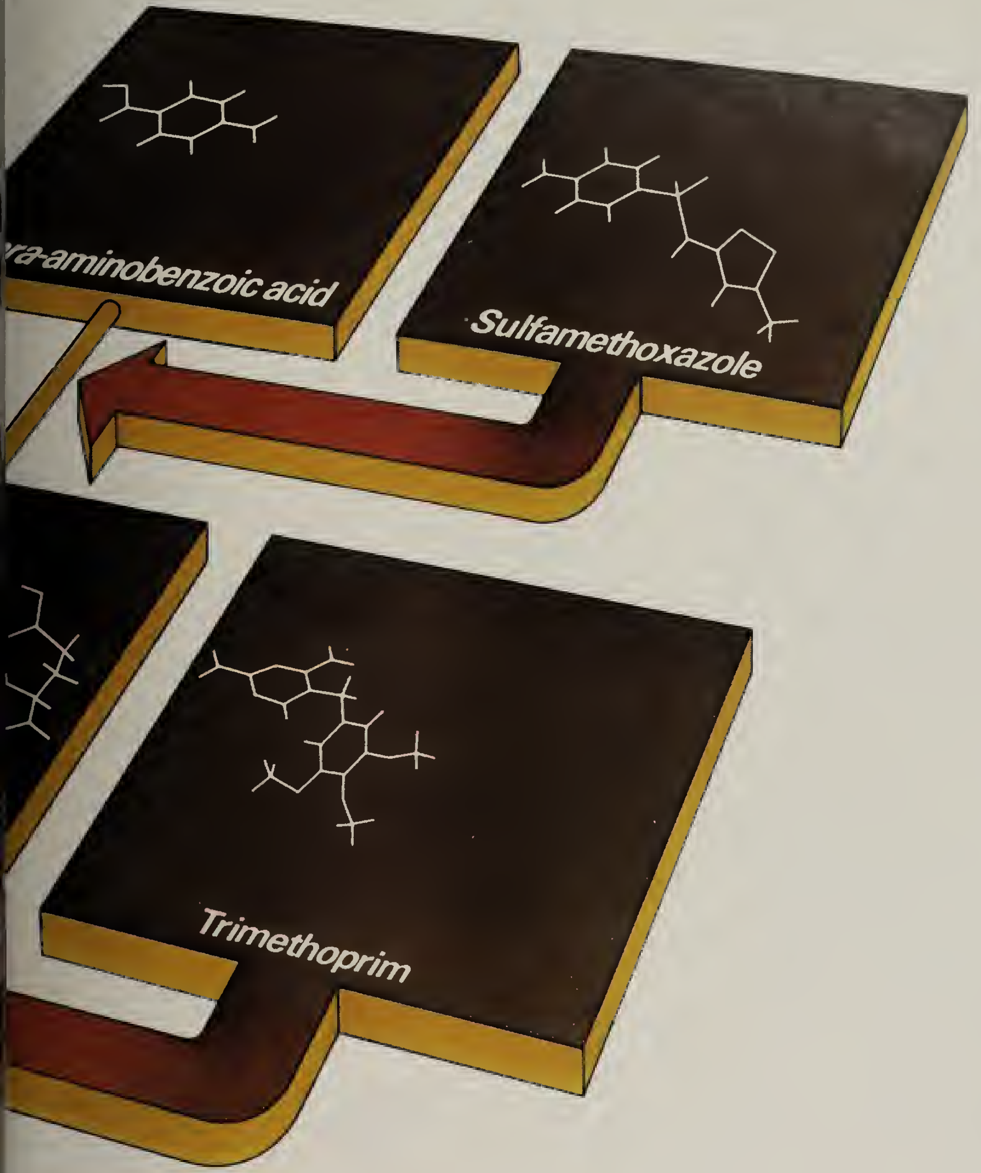
a new type of antibacterial for a two-pronged attack against chronic urinary tract infections due to susceptible organisms

Bactrim is highly effective in the treatment of these infections—primarily pyelonephritis, pyelitis and cystitis—when due to susceptible organisms. This efficacy is related to the unique mode of action against bacteria (see illustration), an action that, in effect, makes Bactrim a new type of antibacterial.

Bactrim interrupts the life cycle of susceptible bacteria

Unique mode of action interrupts the life cycle at two important points, thereby impeding the production of nucleic acids and proteins essential to these bacteria. These consecutive interruptions occur because sulfamethoxazole and trimethoprim resemble naturally existing substrates. By competitive replacement of these substrates, they inhibit further synthesis.




ra-aminobenzoic acid
Sulfamethoxazole
Trimethoprim

ROCHE

new BACTRIM™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

Before prescribing, please see complete product information on last page of advertisement.

Excellent clinical response in chronic urinary tract infections even with obstructive complications

A multiclinic, double-blind study* of response to a ten-day course of therapy in 471† patients with chronic urinary tract infections demonstrated the superiority of Bactrim. On the 10th day after initiation of therapy, 91.7% (of 168 patients) showed significant bacteriological response to Bactrim, compared with 81.2% (of 144 patients) to trimethoprim and 64.5% (of 155 patients) to sulfamethoxazole. More than half of these patients had obstructive complications.

Excellent response maintained

Bactrim proved equally impressive in maintaining this bacteriological response. In the above study, after a ten-day course of therapy with Bactrim, 68.4% of patients with chronic urinary tract infections *maintained* response for up to 42 consecutive days, compared with 59.7% with trimethoprim and 44.4% with sulfamethoxazole. These results are particularly noteworthy considering the number of patients with obstructive complications—cases regarded as being notoriously difficult to treat.

Prescribing considerations

Clinical Limitations: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections. Not recommended for children under twelve.

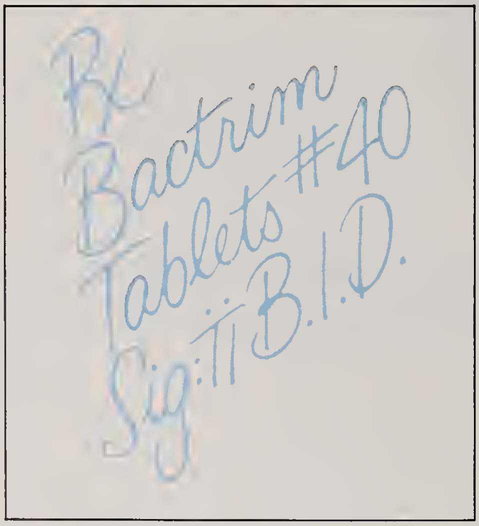
Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period.

Warnings and Precautions: Both sulfamethoxazole and trimethoprim have been reported to interfere with hematopoiesis. Complete blood counts should be done frequently. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued. Bactrim should be given with caution to patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. Maintain adequate fluid intake. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

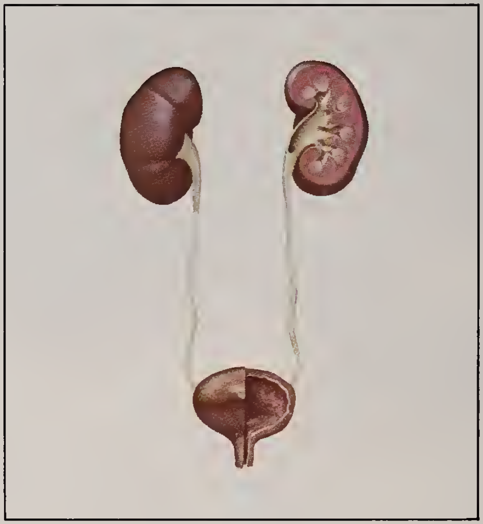
Adverse Effects: Among the most common side effects are nausea, vomiting, rash, leukopenia and elevations in SGOT and creatinine.

Usual adult dosage: two tablets every twelve hours for 10 to 14 days; no loading dose required.

*Data on file, Hoffmann-La Roche Inc., Nutley, N.J. 07110
† 4 patients not available for evaluation at day 10.



Rx
Bactrim
Tablets #40
Sig: ii B.I.D.



new **BACTRIM**™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Before prescribing, please consult complete product information on facing page.

omplete Product Information:

escription: Bactrim is a synthetic antibacterial combination product, available in scored light-green tablets, each containing 80 mg imethoprim and 400 mg sulfamethoxazole.

rimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. is a white to light-yellow, odorless, bitter compound with a molecular weight of 290.3.

ulfamethoxazole is N^1-(5-methyl-3-isoxazolyl)sulfanilamide. It is n almost white in color, odorless, tasteless compound with a molecular weight of 253.28.

ctions: *Microbiology:* Sulfamethoxazole inhibits bacterial synthesis f dihydrofolic acid by competing with *para*-aminobenzoic acid. rimethoprim blocks the production of tetrahydrofolic acid from diydrofolic acid by binding to and reversibly inhibiting the required nzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins ssential to many bacteria.

n vitro studies have shown that bacterial resistance develops more lowly with Bactrim than with trimethoprim or sulfamethoxazole lone.

n vitro serial dilution tests have shown that the spectrum of antibacterial activity of Bactrim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa.* The following organisms are usually susceptible: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis* and indole-positive proteus pecies.

Representative Minimum Inhibitory Concentration Values for Bactrim-Susceptible Organisms
(MIC—mcg/ml)

Bacteria	Trimethoprim alone	Sulfamethoxazole alone	TMP/SMX (1:20) TMP	SMX
Escherichia coli	0.05—1.5	1.0 —245	0.05—0.5	0.95— 9.5
Proteus spp. indole positive	0.5 —5.0	7.35 —300	0.05—1.5	0.95—28.5
Proteus mirabilis	0.5 —1.5	7.35 — 30	0.05—0.15	0.95— 2.85
Klebsiella-Enterobacter	0.15—5.0	0.735—245	0.05—1.5	0.95—28.5

Human Pharmacology: Bactrim is rapidly absorbed following oral administration. The blood levels of trimethoprim and sulfamethoxazole are similar to those achieved when each component is given alone. Peak blood levels for the individual components occur one o four hours after oral administration. The half-lives of sulfamethoxazole and trimethoprim, 10 and 16 hours respectively, are relatively the same regardless of whether these compounds are administered as individual components or as Bactrim. Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. Free sulfamethoxazole and trimethoprim blood levels are proportionately dose-dependent. On repeated administration, the steady-state ratio of trimethoprim o sulfamethoxazole levels in the blood is about 1:20.

Sulfamethoxazole exists in the blood as free, conjugated and protein-bound forms; trimethoprim is present as free, protein-bound and metabolized forms. The free forms are considered to be the therapeutically active forms. Approximately 44 percent of trimethoprim and 70 percent of sulfamethoxazole are protein-bound in the blood. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim to an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Excretion of Bactrim is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. When administered together as in Bactrim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually E. *coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

***Important note:* Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections.**

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see Reproduction Studies).

Warnings: Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Bactrim. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued.

At the present time, there is insufficient clinical information on the use of Bactrim in infants and children under 12 years of age to recommend its use.

Precautions: Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Adverse Reactions: For completeness, all major reactions to sulfonamides and to trimethoprim are included below, even though they may not have been reported with Bactrim.

Blood dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

Dosage and Administration: Not recommended for use in children under 12 years of age.

The usual adult dosage is two tablets every 12 hours for 10 to 14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

How Supplied: Tablets, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 1000; Prescription Paks of 40, available singly and in trays of 10. Imprint on tablets: ROCHE 50.

Reproduction Studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. However, in one study, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

BACTRIM™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N J 07110

Loma Linda
Soyalac
HYPOALLERGENIC
NEW
Soyalac
READY TO SERVE

Colic? Diarrhea? Eczema? Asthma? Rhinorrhea? Fretfulness? Fitful Sleep?

Soyalac is often the answer.

This ailing, wailing syndrome in infants (and older children) is all too familiar. Fortunately, the physician has at his command a trusted ally: milk-free, fibre-free, hypo-allergenic Soyalac.

Soyalac is palatable, readily digested and assimilated. It simulates human milk in appearance, taste, texture. It is complete with vitamins and minerals. It is equally suitable for children and adults allergic to cow's milk.

Through the years Soyalac has proved its value—in promoting growth and development—as attested by extensive clinical data.

Free samples and literature on request.
A simple note on your prescription form will do.

Now available in 3 forms:
Concentrated Liquid,
Ready-to-Serve, Powdered

Soyalac

a product of
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MEDICAL PRODUCTS DIVISION
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Mount Vernon, Ohio 43050, U.S.A.

Upjohn's low-priced erythromycin

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Protect contents from light
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SCIENTIFIC ARTICLES

Hyperfunctioning Thyroid Nodules that Become "Cold"

KENNETH D. BURMAN, M.D., CPT, MC*, RAPHAEL L. WARKEL, M.D., MAJ., MC† AND LEONARD WARTOFSKY, M.D., LTC., MC‡

Two patients were followed who illustrated the phenomenon of change in function in an autonomous thyroid nodule from "hot" to "cold". The changes were spontaneous in both patients and precipitated surgical removal of the nodules because of the fear of an underlying carcinoma.

The state of persistent autonomous function in a solitary nodule has been frequently discussed, and the possible association between maintenance of autonomy and subsequent development of hyperthyroidism has been particularly controversial.

Case Reports

Patient 1:

G.I. was a 32 y.o. white female who presented in May 1970 with the complaint of thyroidal enlargement of indeterminate duration. The history was generally unremarkable with no symptoms suggestive of either hyper- or hypometabolism. There was a strong family history of thyroid disease with nine relatives so affected, five of whom have visible goiters.

Physical examination revealed a well-developed, eukinetic woman. The pulse was 82 and regular, her weight was 113 lbs. The remainder of the examination was negative except for the thyroid which contained a firm 2 x 2 cm. nodule in the middle to upper pole of the right lobe. Initial studies included a T_3 resin uptake (Trisorb) of 29.6% (NL 25-35); a serum T_4 (Tetrasorb) of 7.0 μg% (NL 5-9) and a 24 hour ^{131}I uptake of 15% (NL 12-36). A scintiscan dose 45 minutes after the injection of 1 mc Technetium-99m revealed the nodule to be hyperfunctioning with moderate suppression of the remaining thyroid tissue (Fig. 1A).

The patient was started on dessicated thyroid, 192 mgms/day, in an apparent attempt to determine if autonomous function existed in the nodule. Symptoms of anxiety and tachycardia prompted the patient to decrease the dosage to 128 mgms/day, then to 64 mgms/day, and ultimately to discontinue the thyroid altogether within a month. Recognizing that the nodule was increasing in size, she again sought medical attention in November 1970. The nodule had increased in size and measured 2.5 x 3.5 cm. At this time thyroid function studies included a serum T_4 of 6.4 μg%; T_3 resin uptake of 27%, and a 24 hour radioactive iodine uptake (RAIU) of 23%.

A repeat thyroid scintiscan with 1 mc Tc-99m at this time revealed all thyroid tissue extrinsic to the nodule was now functioning, and paradoxically, that the nodule itself had become completely "cold" (Fig. 1B). On the basis of the findings of an enlarging, single, cold nodule in a 32

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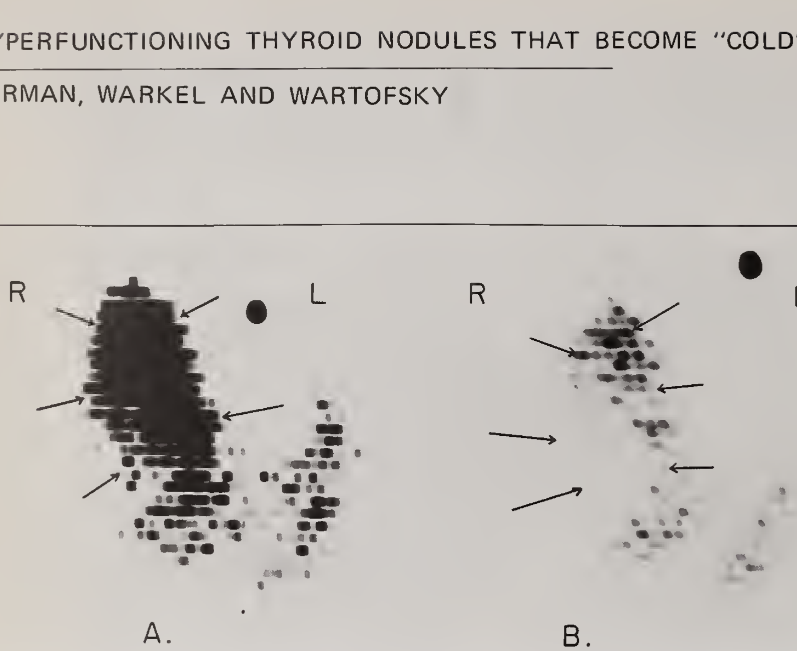

FIG. 1. Both scans were performed after i.v. injection of lmc of Technetium. A. Scan at left shows majority of functioning tissue confined to nodule. B. Repeat scan at right 6 months later. Nodule is now "cold".

y.o. female, surgical excision was recommended. The patient underwent a right thyroid lobectomy in December 1970. Pathologic description of the lesion was of a benign colloid adenoma with areas of focal degeneration, old hemorrhage, and necrosis (Fig. 1C). The patient subsequently recovered uneventfully and is maintaining a euthyroid clinical state on no replacement therapy, with no palpable lesions in the residual left lobe.

Patient 2:

E.C. was a 47 y.o. white female who presented in July 1969 with the complaint of thyroidal enlargement of indeterminate duration. The history was unremarkable with no symptoms suggestive of either hyperthyroidism, hypothyroidism, or thyroiditis. The patient's mother had a goiter for which she was treated with thyroid. Physical examination revealed a well-developed woman with no signs of either thyroid excess or deficiency. The pulse was 84 and regular, her weight was 108 lbs, and the remainder of the examination was negative except for the thyroid gland which contained a 2 x 1.5 cm. nodule located in the middle of the right lobe. The nodule was firm, the thyroid was felt to be otherwise normal.

At this time a 24 hour ^{131}I uptake was 15% (Normal range 12-36%), and a thyroid scintiscan revealed the nodule to be functioning, with partial suppression of the surrounding thyroid. In order to determine if this nodule was autonomous the patient was given dessicated thyroid, 192 mgms daily for three weeks, and the studies repeated. The RAIU was 4% and a repeat scan was not performed.

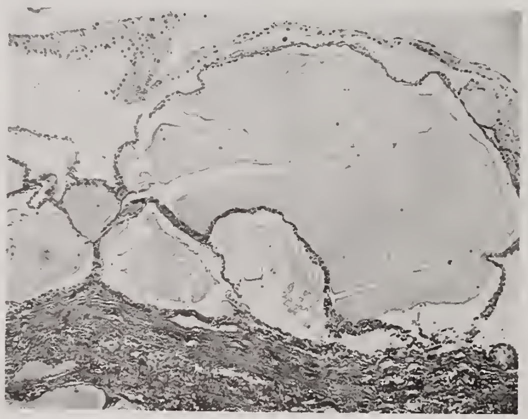

FIG. 1C. Low-power photomicrograph of portion of cystic adenoma found in patient 1.

Because the RAIU response to exo
enous thyroid was thought to rep
sent suppression, she was continued
dessicated thyroid and when seen s
weeks later (17 September 1969) w
complaining of nervousness and tach
cardia with palpitations. A PBI was 5
μg% (NL 4-8) and a T_3 index was 1.
(NL 0.88-1.12), but because of the
complaints, her medication was d
creased to 128 mgms daily.

In November 1969 the nodule w
noted to be increased in size
approximately 2 x 2.5 cm. A repe
scan revealed function only in the ar
of the nodule, with suppression of t
remainder of the gland (Fig. 2A
Thyroid was continued over the ne
five months, and studies in May 197
included a T_4 of 8.8 μg%, T_3 res
uptake (Triosorb) of 31.7% (N
25-35%), and a 24 hour RAIU of 2
demonstrating persistent suppressio

In view of the probable enlarg
ment, and lack of diminution in size
the nodule during suppressive therap
surgical excision was recommended. I
order to ascertain the function
capacity of the left lobe, 10 units
bovine thyroid stimulating hormon
(TSH) was administered intramusc
larly and a repeat scintiscan pe
formed. The scan demonstrated th
the entire left lobe, and the right lob
tissue surrounding the nodule we
stimulated by TSH, but paradoxicall
that the nodule itself had becom
"cold" (Fig. 2B).

A right total lobectomy was pe
formed and pathologic examinatio
revealed a benign thyroid cyst with
fibrotic capsule, containing areas o
hemorrhagic necrosis (Fig. 2C). Th
patient recovered uneventfully an
remains on dessicated thyroid with
normally functioning left lobe and n
palpable nodules.

Discussion

The natural history of a solita
autonomous thyroid nodule (SAN)

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ly variable. With the passage of
e, such a nodule may: 1) demon-
te persistence of autonomy, 2)
onstrate transition from a "hot"
"warm" nodule and still maintain
sistence of autonomy, 3) re-estab-
TSH dependence, or 4) degenerate
h re-establishment of a normal
uitary thyroid axis.[1]

he state of persistent autonomous
ction in a solitary nodule has been
uently discussed, and the possible
ciation between maintenance of
onomy and subsequent develop-
t of hyperthyroidism has been
ticularly controversial.[2] Miller and
ck[2] followed 15 patients with SAN
an average of over three years and
erved that none of the nodules
reciably increased in functional
vity during that period. Of these
patients, four were ultimately
ted for various reasons, including
ht nodule enlargement in one pa-
t, anxiety symptoms in one patient
borderline hyperthyroidism in two
ients. Silverstein, *et al.*,[1] followed
e patients with SAN for an average
e period of four years and none of
se patients developed hyperthyroid-
.

imilarly, of 47 patients with SAN
t we have followed for 4-131
nths (average 23 months), only two
hyperthyroidism at presentation
none developed it during the
ow-up period.

oncerning the possible course of
nsition from a "hot" to a "warm"
lule and re-establishment of TSH
endence, it is difficult to ascertain,
m the literature, how commonly
might occur. Silverstein, *et al.*,[1]
cribed one patient out of the nine
o were followed who demonstrated
h transition from a "hot" to a
arm" nodule, and another one
ient who appeared to have re-estab-
hment of TSH dependence.
tainly, longitudinal studies are re-
red to explore the natural history
the SAN in order to determine the
relative frequency and importance of these potential courses.

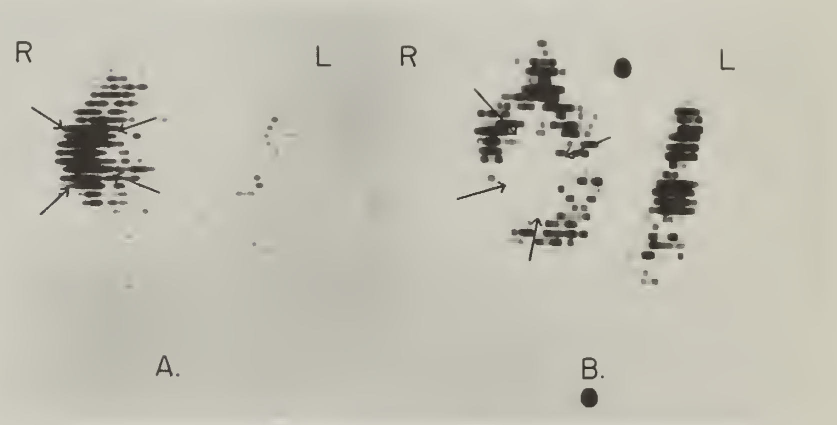

FIG. 2. Both scans performed after lmc TC-pertechnetate. A. Initial scan showing an autonomous nodule with suppression of other thyroid tissue. B. Six months later, following 10 units of TSH the nodule is "cold" on scan and excisional biopsy revealed it to be a benign cyst.

The last of the evolutionary courses for a SAN which was cited was that of degeneration, with re-establishment of a normal thyroid-pituitary axis. This phenomenon often may represent infarction of a hyperfunctioning adenoma with subsequent necrosis and cystic change. Cystic degeneration of a SAN is an unusual occurrence but has been described previously. In their series of nine subjects with SAN, Silverstein *et al.*[1] described one patient who presented with a firm, non-tender nodule in the right lobe of the gland six years after the initial diagnosis had been made. The scan demonstrated iodine concentration within both lobes although the nodule concentrated iodine to a lesser degree than did adjacent thyroid tissue. The patient underwent surgery and pathologic examination of the nodule revealed focal calcification, fibrosis and cystic degeneration.

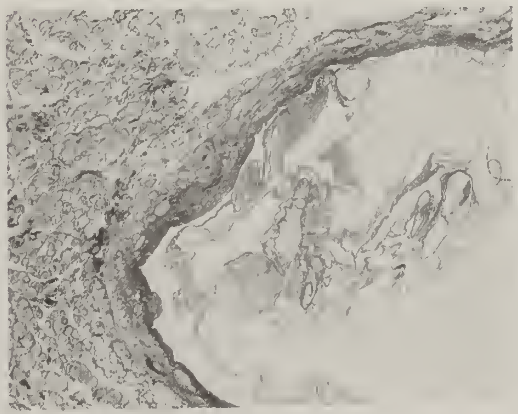

FIG. 2C. Low-power photomicrograph of portion of cystic adenoma found in patient 2. Note normal follicular tissue outside of cyst wall and degenerating follicles with old hemorrhage within the cyst.

Blum and Nocero[3] described a 19 year old female who had a SAN which was asymptomatic for two years, but then manifested pain and further swelling. Subsequent scintiscans revealed loss of autonomous function of the thyroid gland and decreased function in the area of the thyroid nodule, but cystic degeneration of the SAN was not verified on pathologic examination.

Degenerative changes in a follicular adenoma may consist of hemorrhage, infarction and fibrosis. The development of a cold area in a previously hot nodule would suggest such a change and would be of minor concern were it not for the fact that carcinoma may present in identical manner. An increase in the size of a cold nodule, particularly while a patient is receiving thyroid therapy, is generally considered an immediate indication for surgery. It was in this light that the enlargement of the nodules in the presently reported patients was viewed.

Patient E. C. illustrates the phenomenon of non-responsiveness of an SAN to exogenous TSH (Fig. 2B).

In this regard, Miller, *et al.*[2] found that autonomous tissue tended to respond less well to TSH than did normal, suppressed thyroid tissue. More recently, Ashkar and Smoak suggested that cold areas might be present in a high proportion of autonomous nodules which often may not respond to TSH, thus giving the scintiscan the appearance of an "owl eye"[4].

As described, the nodules in both our patients were found to be degenerating cysts, and accumulation of cystic contents was the probable explanation for their progressive enlargement. Although carcinoma is only rarely associated with solitary autonomous nodules, there is little data at present on the likelihood of malignancy in the setting described in the present report [5]. Until this information is available, we might caution that cold areas on scintiscan developing in an autonomous nodule may represent a benign process rather than neoplasia, and therefore conservative management with observation may be warranted. The likelihood that hemorrhage and necrosis had occurred in a benign lesion would be further strengthened by the finding of concentric calcifications within the nodule on soft tissue X-rays of the neck.

Summary

Two patients are reported in whom hyperfunctioning thyroid adenomas enlarged and became cold on scintiscan, raising the question of malignancy, but which were found to be only cystic on pathologic examination. It is possible that such a phenomenon may be relatively common and confirmation of the frequency of this event in the future may permit conservative management with continued observation of such nodules rather than surgical intervention.

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Adrenal Insufficiency Resulting from Metastasis of Non-Functioning Adrenocortical Carcinoma

HUNTER HEATH III, M.D.* AND PATRICK R. BERGEVIN, M.D.†

Metastatic tumor to the adrenal glands rarely produces functional impairment of the adrenal cortex.[2,7] The following case report describes a patient with metastatic non-functioning adrenocortical carcinoma[6] in whom adrenal insufficiency developed.

Case Report

W. J., a 51 year old white male, was in excellent health until January 1965, when he was referred to Walter Reed General Hospital (WRGH) for evaluation of low back pain. A left upper quadrant abdominal mass was incidentally discovered, and a retrospective history obtained of a 25 lb weight loss in the preceding year. The patient was otherwise asymptomatic. Exploratory laparotomy was performed, with the finding of a 17 by 19 cm hemorrhagic mass replacing the left adrenal gland; the microscopic appearance (Figs. 1 and 2) was that of adrenocortical carcinoma. After surgery the patient regained his usual weight and felt well. Six months postoperatively, the 24 hour urinary 17-hydroxycorticosteroids were 4.3 mg and 17-ketosteroids 8.8 mg.

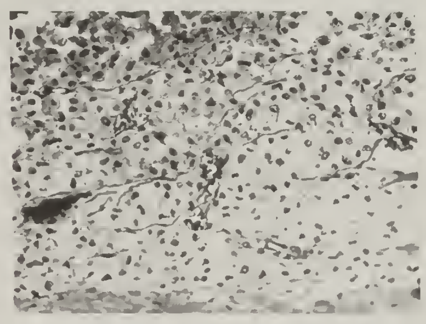

FIG. 1. Primary adrenocortical carcinoma. In areas such as this the cells are arranged in cords resembling adrenal zona fasciculata. Degenerative changes are seen at upper left, tumor capsule at bottom. H and E X196. AFIP neg. #72-9430.

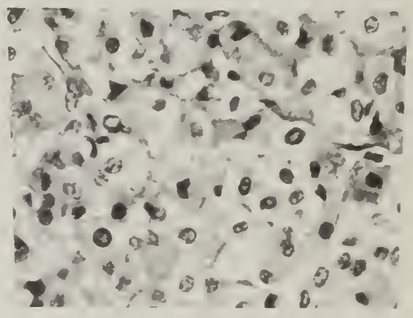

FIG. 2. Primary adrenocortical carcinoma. The appearance of the cytoplasm is variable: most cells are eosinophilic and somewhat granular, while others are pale-staining and vacuolated. Many cells contain neutral lipid on special staining. H and E X530. AFIP neg. #72-9431.

In September 1965, the patient returned to WRGH for evaluation of hypertension (as high as 190/130), but no etiology could be found. Methyl dopa was prescribed briefly, then discontinued without recurrence of significant hypertension.

Low back pain radiating down the lower extremities persisted. Unexplained episodes of left upper quadrant abdominal pain occurred, prompting exploratory laparotomy at another hospital in December 1967, which revealed enlarged lymph nodes in the left upper quadrant containing adrenocortical carcinoma.

In January 1968, the patient was re-evaluated at WRGH. His weight was stable at 195 lbs and his blood pressure was 136/84 on no anti-hypertensive medications. Examination revealed no abdominal masses. Twenty-four hour urine 17-OHCS determinations on two occasions were 10.5 and 3.8 mg, and 17-KS determinations 11.9 and 17.7 mg.

In February 1969, because of increasing back pain, the patient underwent lumbar laminectomy and removal of a herniated nucleus pulposus, with permanent relief of the symp-

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The presence of a tumor in the area of the remaining adrenal gland, together with failure of ACTH stimulation a month after discontinuation of prior chemotherapy, suggests that metastatic disease was responsible for our patient's adrenal failure.

toms related to it. A chest radiograph for the first time revealed nodular lung metastases. The 24 hour urinary 17-OHCS was 4.3 mg. In November 1969, chemotherapy was instituted with 5-fluorouracil (15 mg/Kg/week intravenously) and continued until July 1970, when progressive enlargement of his lung nodules and appearance of hepatic enlargement were noted.

Over the next year the patient noted progressive weight loss, episodic left upper quadrant abdominal pain, weakness and several episodes of syncope. During this time he was treated with courses of hexamethylmelamine, cyclophosphamide and methotrexate, bleomycin and adriamycin, and high dose methotrexate with leukovorin factor reversal followed by cytosine arabinoside infusion, all without response.

In August 1971, he was admitted to the hospital because of persistent nausea and vomiting, and postural hypotension occurring over a period of approximately four weeks. His weight was 150 lbs, the supine blood pressure 88/56, the pulse 106/min. Laboratory data included serum sodium 131 mEq/l, potassium 5.7 to 6.3 mEq/l, chloride 95 mEq/l, CO_2 21 mEq/l, BUN 23 mg/100 ml, creatinine 1.0 mg/100 ml, WBC 10,700/mm^3, eosinophil count 75/mm^3. The possibility of adrenal insufficiency was considered; a plasma cortisol drawn at 8:00 a.m. (Porter-Silber chromogens) was 21 meg/100 ml (normal, 8-18 meg/100 ml). This value is inappropriately low considering the patient's clinical status. The patient was treated initially with large doses of cortisol intravenously (400 mg in the first 24 hr) and saline infusions with striking subjective and objective improvement. Within two weeks of instituting cortisol therapy the patient had gained 10 lbs in weight, the blood pressure was 110/70 without postural fall, the serum sodium was 135 mEq/l and serum potassium 4.0 mEq/l.

One month after initiation of treatment for adrenal insufficiency, the patient was admitted to the WRGH Metabolism Research Ward for study. Cortisol had been replaced with dexamethasone, 0.75 mg/day for four days prior to and during testing. After two days of control urine collections, ACTH (Corticotropin injection, U.S.P., Armour Pharmaceutical Co.), 40 units, was given intravenously from 8:00 a.m. to 4:00 p.m. on each of four consecutive days. Plasma and urine steroid values from the study are given in Table 1. There was no significant increase in plasma or urine cortisol levels during ACTH infusion, confirming primary adrenal insufficiency.

An intravenous pyelogram with nephrotomography (Courtesy of Dr. E. C. Dunn, Somers Point, N. J.) showed marked caudad and anteromedial displacement of the right kidney by a rounded, indistinct soft-tissue mass at least 11 cm in diameter. There was no evidence of a left suprarenal mass.

Discussion

Adrenocortical carcinoma is known to metastasize to originally normal adrenal glands;[3,5] interference with adrenocortical function, however, has not been previously demonstrated. Our patient developed a large right suprarenal mass nearly seven years after diagnosis of his primary tumor, and while we do not have histologic proof that the mass is composed of adrenocortical carcinoma, there is no other ready explanation. Typical clinical signs and symptoms of adrenocortical insufficiency were attributed to effects of cancer and its therapy until the development of frank hypotension, hyponatremia and hyperkalemia. The striking response to steroid therapy plus the almost total failure of ACTH stimulation clearly establish a diagnosis of primary adrenal insufficiency. While tests of adrenocortical function were not done before this patient's primary tumor was removed, the failure to show elevation of 17-OHCS or 17-KS excretion at any time in the subsequent clinical course, in the presence of frank metastases, suggests that his tumor did not produce significant quantities of biologically active corticosteroids.

The use of multiple chemotherapeutic regimens in this patient raises the question of drug-induced adrenocortical failure. The patient has never received o,p'-DDD[4,10] or aminoglutethimide[1], drugs which do indeed alter synthesis of adrenal corticoids. Fluorouracil has been reported to inhibit adrenal responsiveness to ACTH,[9] but our patient had not received the drug in many months at the time adrenal failure became manifest. We are unaware of evidence that the other chemotherapeutic agents used (methotrexate, cytosine arabinoside, bleomycin, adriamycin, cyclophosphamide and hexamethylmelamine) can impair adrenocortical function. The presence of a tumor in the area of the remaining adrenal gland, together with failure of ACTH stimulation a month after discontinuation of prior chemotherapy, suggests that metastatic disease was responsible for our patient's adrenal failure.

Roginsky and Schick[8] reported a patient with functioning adrenocortical carcinoma and hypoadrenalism following therapy with o,p'-DDD and

5-FU; interestingly, their patient also had a large mass in the remaining adrenal gland. While the authors state that chemotherapy was responsible for adrenal insufficiency in their patient, we suggest that massive metastasis to the normal adrenal gland may have played a role as well.

This report documents that metastasis of adrenocortical carcinoma to the opposite adrenal gland, reported to occur in up to 12% of cases,[5] may destroy the function of the remaining normal adrenal tissue. This was of clinical importance in our patient because his tumor did not produce detectable steroid hormones, but would be of equal importance in the event of successful therapy of functioning adrenocortical carcinoma. While this must be a rare occurrence,[7] it deserves recognition in centers caring for large numbers of patients with malignancies; simple replacement steroid therapy is lifesaving.

Acknowledgments

We are grateful for the advice and encouragement of Jerry M. Earll, M.D., Col., MC and Johannes Blom, M.D., and for the able secretarial assistance of Eleanore D. Ritter. James E. Oertel, M.D., of the Armed Forces Institute of Pathology kindly assisted in interpretation and photography of the slides.

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TABLE 1

Four-day ACTH Stimulation Test. See text for methods and interpretation.

	Urine Corticosteroids		Plasma Porter-Silber Chromogens	
	(mg/24 hr)		(μg/100 ml)	
Day	17-OHCS	17 KS	Pre-ACTH	Post-ACTH
Control–1	0.8	12.9	–	–
Control–2	0.6	14.3	–	–
ACTH-1	1.0	14.7	–	7.4
ACTH-2	1.4	11.5	6.0	9.5
ACTH-3	1.5	12.2	6.0	10.5
ACTH-4	1.3	11.5	6.5	9.5

Metastases in Bone Marrow and Pancytopenia from Carcinoma of the Lung (Report of a patient and review of the literature)

MAJ. IVAN P. LAW, M.D., MC, U.S.A.R.*

Abstract

A patient is presented with pancytopenia with a cellular marrow with marked granulocytic immaturity resembling early myeloblastic leukemia. Eight months later he developed recurrent lung abscesses and died with squamous cell carcinoma of the lung with bone marrow metastases. Cases with pancytopenia and cellular marrows as a clinical entity will be reviewed and the possible etiology will be discussed.

Introduction

Anemias due to marrow replacement by metastatic carcinoma are usually that of myelophthisic anemia with leukoerythroblastic peripheral blood pictures[1,2,3]. Occasional cases have been reported with leukemoid reactions[4,5], and pure red cell aplasia[6,7]. We have recently observed a patient with bronchogenic carcinoma who presented with pancytopenia, a left shift of his cellular marrow and recurrent pulmonary abscesses.

. . . the incidence of sternal marrow metastasis with bronchogenic carcinoma is as high as 34%, but with adequate marrow reserve.

Report of the Case

A 58 year old black male was admitted on Feb 9, 1972, with the chief complaint of chronic cough, sore throat and shortness of breath on exertion. His past history included a normal CBC on physical examination in November 1971. The pertinent physical findings were of a thin male, weighing 117 lbs, 5′ 7″ in height, with a blood pressure of 120/80, temperature of 98.6 F., a pulse of 80/min. He had no evidence of jaundice, purpura, lymphadenopathy, or splenomegaly. Chest and cardiac examinations were normal. The laboratory showed a normal urinalysis, a hemoglobin of 11.7 gm%., Hematocrit of 37%, RBC 3.26 million/ cu mm., WBC 3400/cu mm, with the differential count: neutrophils 11%, lymphocytes 85%, eosinophils 2%, monocytes 2%. The smear showed normocytic, normochromic red cells. Platelet count was 50,000/ cu mm., reticulocyte count 1.6%. Bone marrow aspiration from the posterior iliac crest showed a normocellular marrow. Megakaryocytes were present although in slightly reduced numbers. Erythroid activity appeared to be normal with megaloblastoid maturation. The granulocytic series revealed almost complete absence of mature forms with increased numbers of myeloblasts and myelocytes (Fig. 1). Direct and indirect Coomb's antiglobulin tests were negative. Leukocyte alkaline phosphatase activity was normal (score 103). A sickle cell preparation was negative. The screening test for G-6PD deficiency was normal. The serum iron was 123 μg%., serum iron binding capacity 213 μg%. Uric acid was 4.1 mg%. Urine for Bence Jones protein was negative. Serum protein electrophoresis was normal. The screening tests for paroxysmal nocturnal hemoglobinuria were negative. Hemoglobin electrophoresis was normal. Stools for occult blood were negative. Roentgenographic studies of the chest, intravenous pyelogram, skeletal surveys, barium enema, gastrointestinal and small bowel series were normal. Sputums for cytology were negative. The patient was sequentially treated with ferrous sulfate, folic acid, B-12 and pyridoxine, without any appreciable response.

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He was readmitted on September 20, 1972 for lung abscess. The chest roentgenogram showed a right upper lobe abscess cavity with a prominent right hilar mass (Fig 2). The hematologic studies revealed pancytopenia (Table 1). Leukocyte antibodies studies were negative. Serum calcium was 9.5 mg%. Serum alkaline phosphatase was normal. Sputum culture grew Klebsiella and Pseudomonas aeroginosa. Sputum cytology study was negative. Bronchoscopic and mediastinoscopic examinations, including bronchial biopsy and bronchial washings, revealed no tumor cells. Sternal marrow aspiration revealed a "dry tap". The sternal marrow trephine biopsy was done lastly and revealed massive replacement of marrow by tumor tissue (Fig 3).

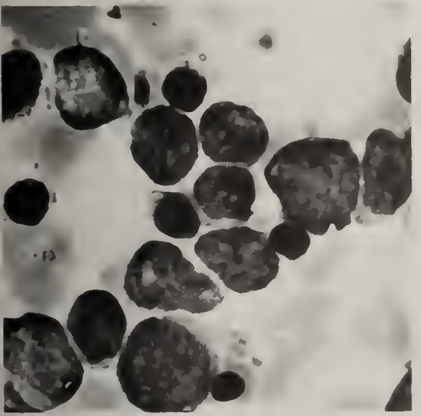


FIG. 1. Bone marrow smear showing myeloblasts and maturation block of leukocyte elements. (Wright's stain, magnification, X 1500, oil immersion).

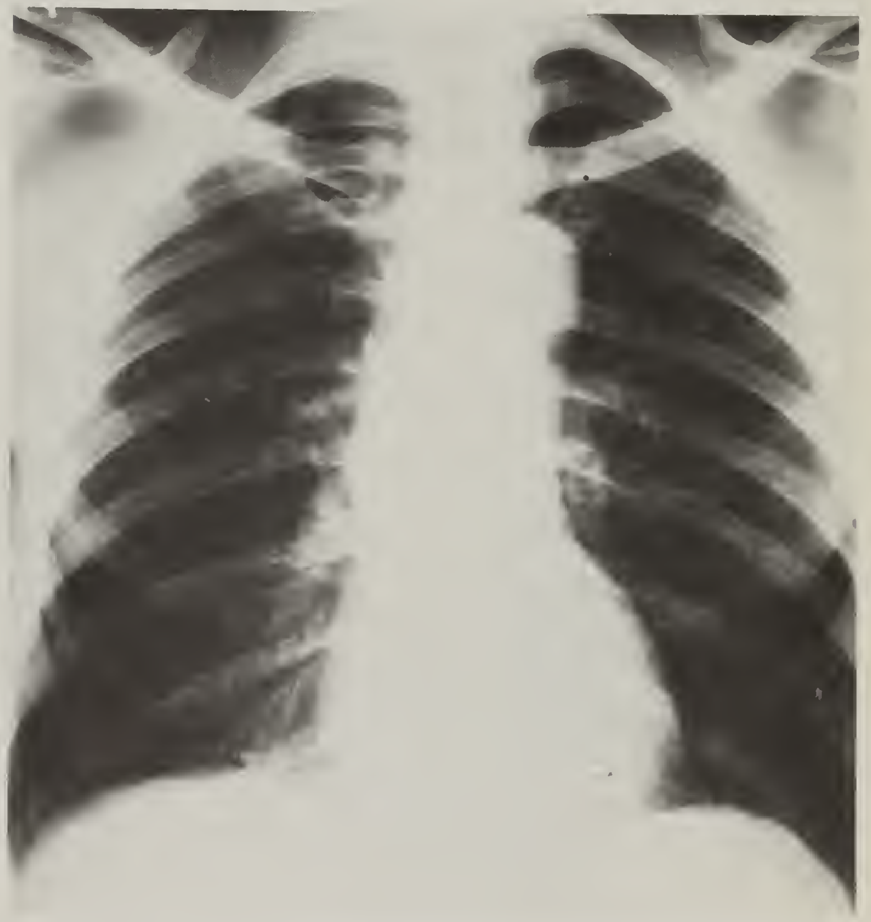


FIG. 2. Chest films obtained at the beginning of illness (above) and 8 months later (next page). (Note–An abscess cavity in the upper lobe of right lung with enlarging right hilar mass).

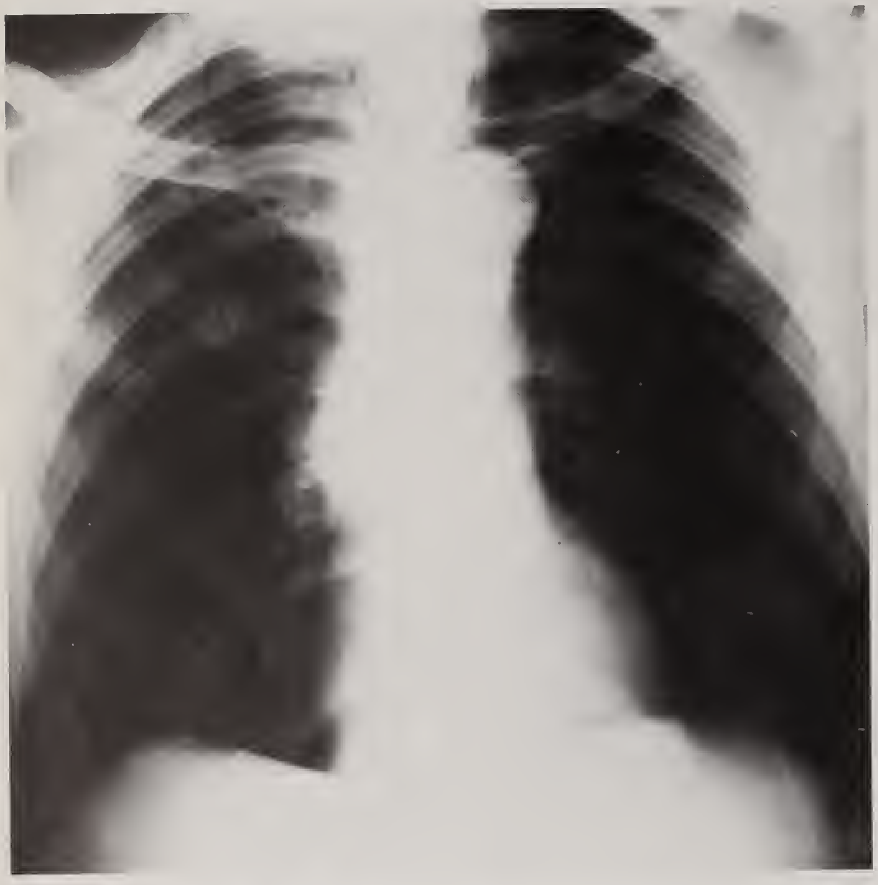
Skin reactions to tuberculin monilia antigen (1:100 dilution, Hollister-Stier lab), Trichophyton antigen (Hollister-Stier lab), and Varidase (Streptokinase-Streptodornase, Lederle) were all negative.

The quantitative immunograms, utilizing an immuno-diffusion method (C Behring, Tri-Partigen, commercial plate accupak system), were normal.

The patient expired 2 months later and the postmortem examination revealed squamous cell carcinoma from the right upper lobe bronchus (Fig 4) with residual lung abscess, and tumor metastases in sternum and spine, but without metastases to the ilium.

Discussion

The occurrence of pancytopenia with cellular marrow secondary to a maturation defect, associated with metastatic carcinoma, has not been reported previously in the literature. This complication appears to be rather rare, although the incidence of sternal marrow metastasis with bronchogenic carcinoma is as high as 34%[8], but with adequate marrow reserve. This clinical entity of pancytopenia with cellular marrow had been observed previously.



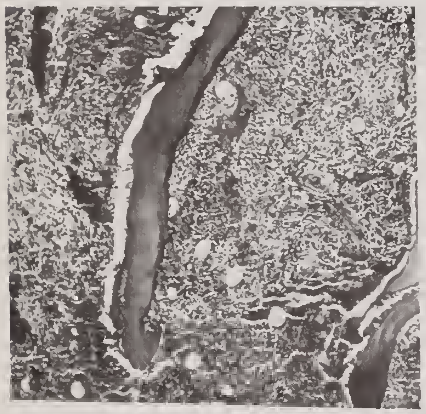


FIG. 3. Section of sternal marrow showing diffuse invasion of the marrow by sheets of malignant cells. (Hematoxylin and eosin, magnification, × 100).

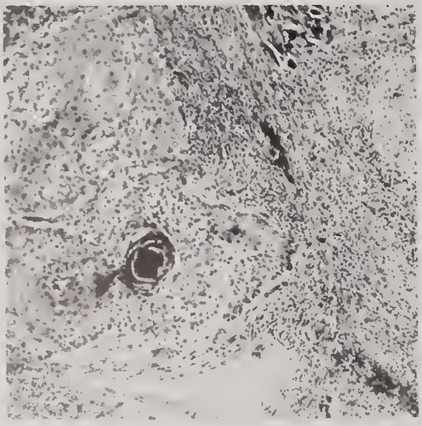


FIG. 4. Squamous cell carcinoma from the right upper lobe bronchus. (Postmortem) (Hematoxylin and eosin, magnification × 100).

Pancytopenia with a cellular marrow may represent a pre-malignant condition. Mallory, Gall, and Brickley in 1939[9] reported a case of erythroleukemia developing in the course of refractory anemia secondary to chronic Benzol poisoning and, in 1953, Block, Jacobson, and Bethard[10] described this state as a preleukemic phase of acute leukemia. Lange[11] in 1955, reported the similar clinical picture in persons who had been exposed to irradiation from the atomic bomb. In 1967, Vilter[12] described 12 cases under the title of type III refractory anemia. In this series, ten patients had a malignant course and died in six to 24 months with myeloproliferative syndromes, such as myelomonoblastic leukemias, panmyelosis with myelofibrosis, or aplastic anemia.

Schiller, M. and associates[13] recently described 28 cases of pancytopenia with cellular marrow in patients with non-malignant conditions. Eleven patients were on various drugs such as Chloromycetin, sulphonamides, Phenylbutazone, Phenacetin, and Dipyrone in various dosages at varying intervals. In their series, no patient had a response to B-12, folate, cobalt, pyridoxine or androgenic steroids administered for prolonged periods. However, temporary therapeutic benefit was obtained in most instances with corticosteroids (Prednisone) or corticotropin. Of the 28 patients, 11 patients died within five months to ten years and postmortem on seven cases revealed hemorrhages in three, bacterial sepsis in three and candida septicemia in one.

In our patient, the etiology of the pancytopenia with a cellular marrow and marked granulocytic immaturity resembling early myeloblastic leukemia is uncertain. It is not due to replacement or destruction of marrow elements by tumor tissue as adequate marrow reserve was seen at postmortem examination. Because the pa-

TABLE 1

HEMATOLOGIC STUDIES DURING THE COURSE OF ILLNESS

	1971	1972						1973
Date	11/12	2/9	3/15	5/11	9/21	10/10	12/21	2/4
Hb. G/100 ml	13.8	11.7	12.1	11.1	7.1	10.6	7.3	7.4
Hematocrit %	42	37	37	34	21	31.8	21.2	23.3
RBC x106/mm^3	–	3.26	3.4	–	–	3.2	2.25	2.3
Reticulocyte Count %	–	1.6	–	–	–	1.5	1.5	–
WBC/mm^3	5400	3400	2500	1900	1290	2600	1700	2200
Neutrophils	–	11	15	18	5	19	16	4
Lympho Monocytes %	–	89	85	82	95	81	84	96
Platelets x103/mm^3	–	50	80	55	20	38	30	–

tient presented initially with neutropenia (Table 1), white cell antibody studies[14,15,16] were performed and were negative. We are unaware of pancytopenia with cellular marrow occurring on an autoimmune basis. The possibility of a preleukemic stage of acute leukemia[17,18,19] cannot be excluded in the initial stage of his illness; however, there was no evidence of leukemia at the postmortem examination. In addition our patient was on no drugs known to induce pancytopenia as described by Schiller and associates[13]. The patient was treated with carbenecillin, gentamycin, penicillin, and cephalothin for recurrent pulmonary abscesses in the terminal phase of his illnesses only. We are left to postulate that squamous cell carcinoma of the lung caused ineffective marrow production and/or a maturation defect.

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THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center

24 year old black male complains about difficulty in swallowing for most of adult life. Recently he had a "sore throat" with increase in symptoms and this brought him to medical attention. He denied any respiratory symptoms. On examination there was a hard, fixed mass, 7 cm. in diameter on the left involving the tonsillar region and extending inferiorly to the vallecula. There was no adenopathy and routine laboratory tests were WNL.

Lateral and frontal radiographs, including tomograms, were obtained.

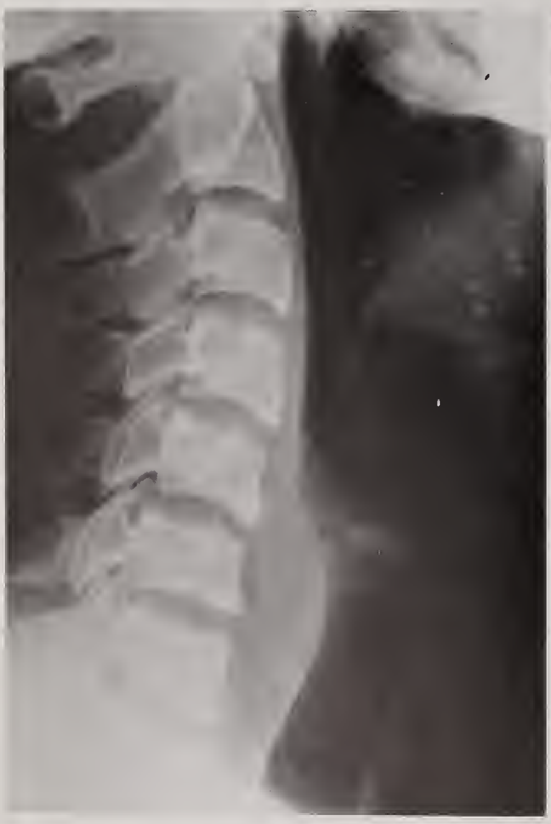

Fig. 1

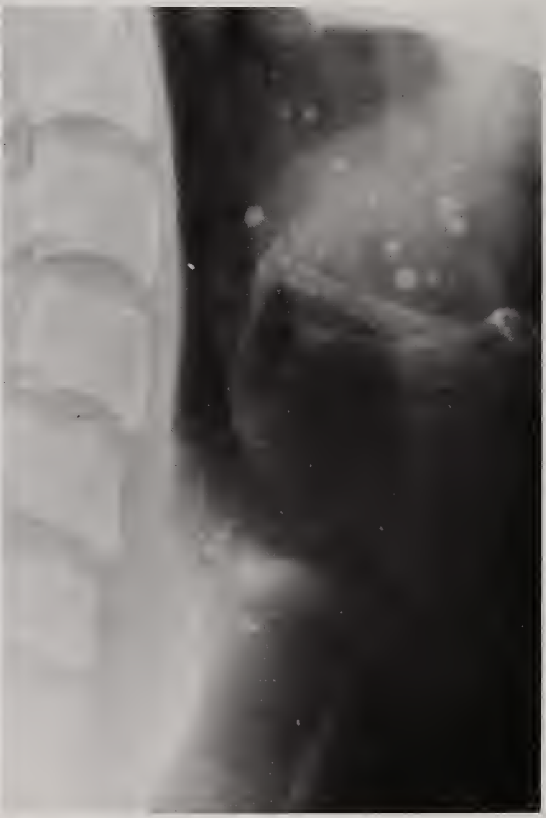

Fig. 2 (conedown)

(for diagnosis see page 558)

Dysphagia Lusoria: A Forgotten Entity?

RICHARD C. CAMMERER, M.D., MAJ., MC*

Bayford[1] in 1787 described in detail the case history of a patient who died of starvation after having suffered from dysphagia of increasing severity for many years. Post-mortem examination revealed an aberrant subclavian artery which arose from the left side of the aortic arch and coursed between the esophagus and the trachea to supply the right arm. Concluding that the anomalous vessel produced dysphagia by compressing the esophagus, Bayford described his findings as a *lusus naturae* or freak of nature. The term dysphagia lusoria has since been used to describe symptomatic esophageal compression by an anomalous right subclavian artery. This diagnosis, which should be considered in all cases of dysphagia, can be established radiographically and endoscopically with relative ease. The following case recently evaluated at Walter Reed Army Medical Center is presented to illustrate this point.

The term dysphagia lusoria has since been used to describe symptomatic esophageal compression by an anomalous right subclavian artery.

Case Report

H. P., a 20-year-old white male sought medical attention after experiencing mild dysphagia for six months. Difficulty swallowing first was noted following recovery from a dental abscess which had forced him to restrict his intake to liquids and soft foods. Upon resuming a regular diet he experienced the sensation of temporary arrest of solid boli at the level of the manubrium. Although he experienced no other symptoms and the severity of his dysphagia did not progress, he became extremely anxious and fearful that a malignant lesion was producing his symptoms.

A barium esophagogram revealed a characteristic filling defect (Figures 1A & 1B). Esophagoscopy with the ACMI panendoscope (model #FO-7089P) revealed a 1.0 cm. extrinsic pulsatile mass along the posterior aspect of the esophagus 20-21 cm. from the incisor teeth. The aortic indentation was visualized along the left anterior aspect of the esophagus at a distance of 23-24 cm. Compression of the proximal pulsating mass with the tip of the endoscope resulted in obliteration of the patient's right radial pulse. The pulse returned immediately after the endoscope tip was withdrawn. This procedure confirmed the suspected diagnosis of an aberrant right subclavian artery. An arteriogram (Figure 2) demonstrated the anomalous right subclavian artery and revealed an unexpected common origin of the carotid arteries. A detailed explanation of the barium esophagogram, angiogram and the endoscopic findings proved effective in allaying the patient's anxiety.

Discussion

Although an anomalous right subclavian artery is common, symptomatic manifestations are rare. However, since this aberrant artery can produce dysphagia it should be considered in the differential diagnosis of this symptom. The aberrant artery arises directly from the posterior aspect of the distal aortic arch just beyond the origin of the left subclavian artery and courses to the right in one of three ways. It passes behind the esophagus in 80% of cases, between the esophagus and trachea in 15% or anterior to the trachea in 5%[7]. Postmortem studies indicate an aberrant right subclavian artery is the most common anomaly of the aortic arch system with an incidence of 0.6-1.8%[3].

Symptomatic patients most frequently present with a feeling of food sticking transiently at the level of the manubrium sterni. The dysphagia is generally insidious and may be mild and intermittent or more often mild and unrelenting. Most of the patients in one series had been symptomatic

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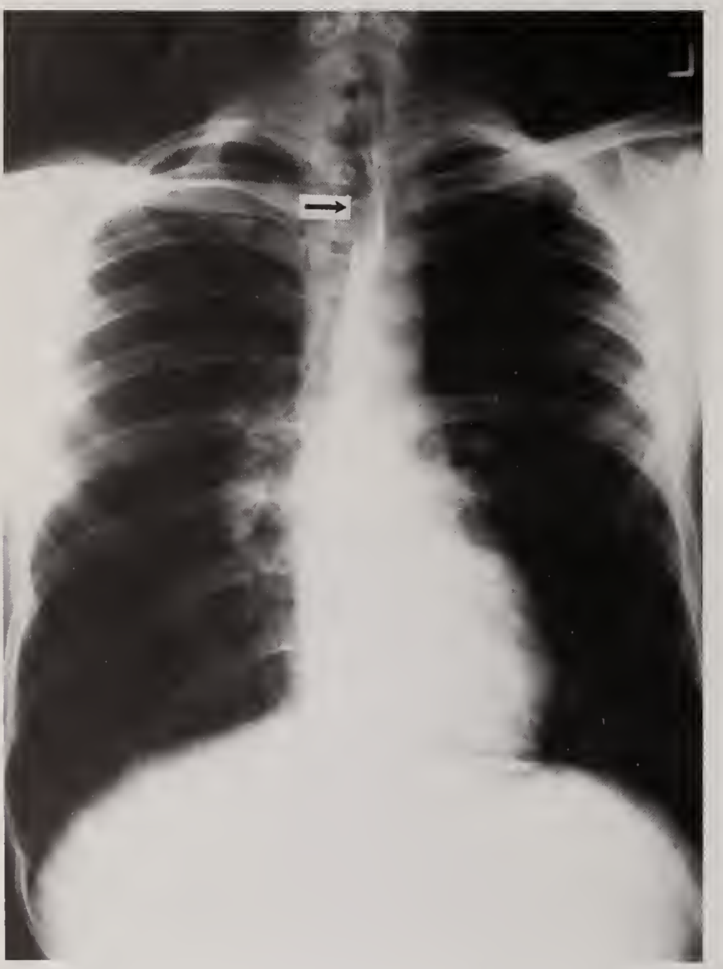

FIG. 1A. Arrow indicates esophageal compression defect produced by aberrant subclavian artery.

for more than one year at the time the diagnosis was established[3]. Pain other than the discomfort of substernal fullness which usually accompanies obstructed swallowing does not occur. Palmer[3] found that patients in his series also regularly mentioned the symptoms of disability, fear and fatigue.

Physical examination yields no specific findings which can establish the diagnosis.

Apart from the clinical presentation, there are three diagnostic approaches which may be used to establish the presence of an aberrant artery. The characteristic deformity on barium swallow is easily recognized. The anomalous vessel produces an indentation on the posterior aspect of the esophagus as it passes obliquely upward and to the right. The radiologic defect typically appears at the level of the third or fourth thoracic vertebra just above the aortic arch.

Angiography demonstrates the origin and path of the anomalous vessel in addition to other vascular malformations which are often present.

Esophagoscopy reveals in most cases a pulsatile extrinsic pressure deformity along the posterior aspect of the proximal esophagus, 20-21 cm. from the incisor teeth. Manipulation of the tip of the endoscope against this pulsatile mass will often obliterate the right radial pulse[1]. Additionally, esophagoscopy is helpful in eliminating other esophageal disorders which may cause dysphagia.

Explanation of the radiographic findings and reassurance provides ade-

medical annals of the district of columbia

vol. 42 no. 11 november 1973

quate therapy in most cases[3]. Surgical intervention, however, may be required in patients experiencing progressive debilitating dysphagia[1,2,4,5,6].

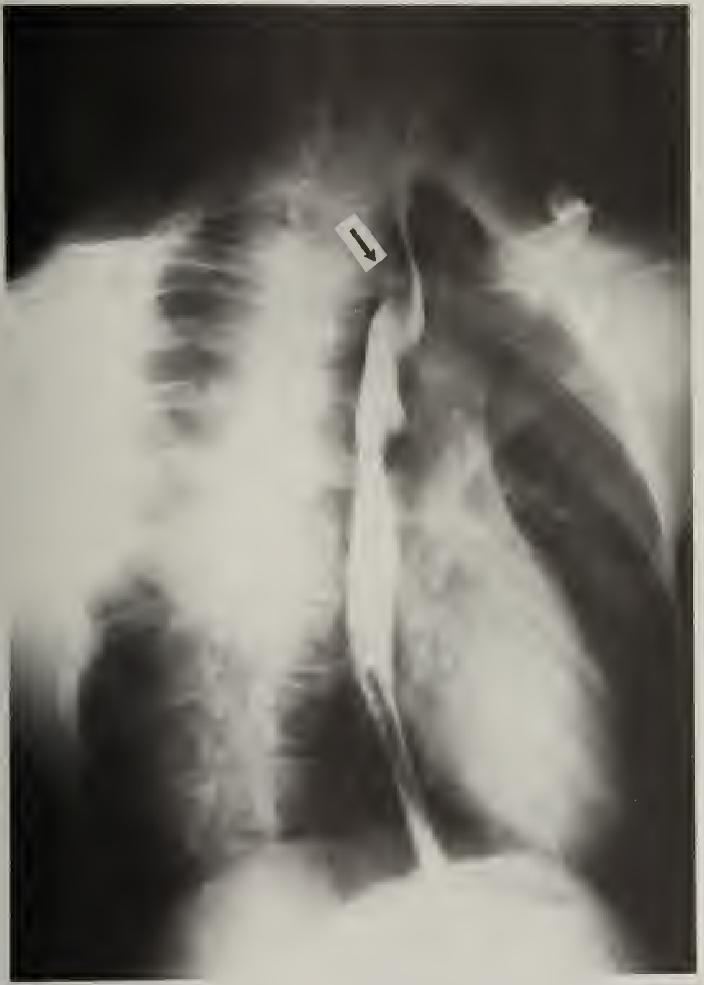

FIG. 1B. Arrow indicates compression defect seen on the right anterior oblique film. Note anterior compression defects produced by aortic arch and left mainstem bronchus below this level.

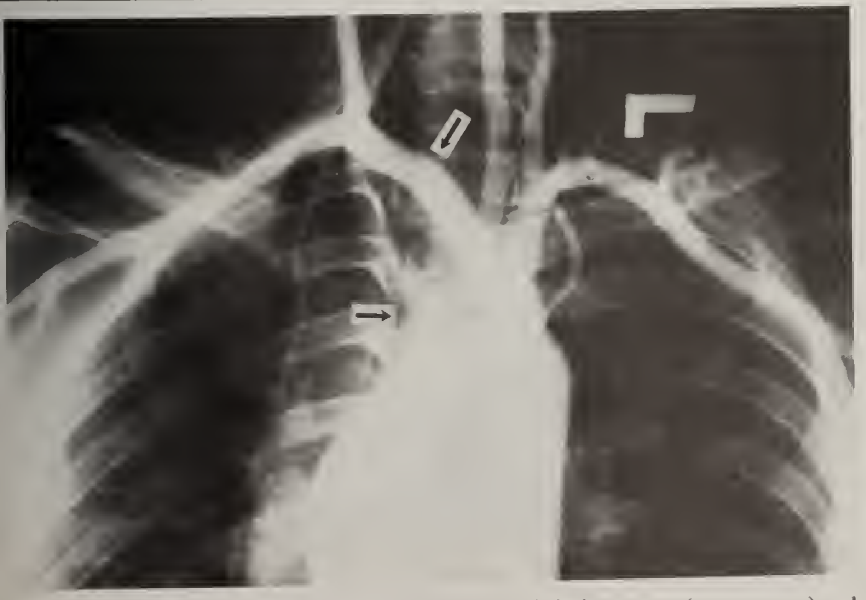

FIG. 2. Angiogram revealing the anomalous right subclavian artery (upper arrow) and the common origin of the carotid arteries (lower arrow).

Conclusion

Dysphagia lusoria, which may be more common than ordinarily appreciated, results from compression of the esophagus by an anomalous right subclavian artery. The diagnosis can be established easily by history, radiographic studies and endoscopic examination. Reassurance in most cases will provide satisfactory therapy. Surgical intervention in severely symptomatic patients may be required.

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^{99m}Tc Sodium Pertechnetate Scanning of the Abdomen, A Valuable Tool for Detection of Meckel's Diverticulum

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Introduction

Peptic ulceration of the ileal mucosa adjacent to a Meckel's diverticulum is one of the main causes of lower gastrointestinal bleeding in childhood. Even though only one fifth of these diverticula contain gastric mucosa, they are the ones most likely to be clinically significant. Bleeding is the most common complication calling attention to this anomaly. The heterotopic gastric mucosa has the capacity of secreting hydrochloric acid and will concentrate the isotope ^{99m}Tc sodium pertechnetate. This case report illustrates how this relatively simple radioisotope procedure led to the correct preoperative diagnosis in a 16-year-old boy with recurrent episodes of rectal bleeding.

Case Report

A 16-year-old boy first noted mild, cramping periumbilical pain followed by passage of bloody stools in February 1973. Symptoms continued for three days with development of weakness and dizziness and he was hospitalized. Diagnostic studies included a normal proctosigmoidoscopy, upper gastrointestinal series with small bowel follow through and barium enema. Recovery followed cessation of bleeding and transfusion with two units of blood. He remained asymptomatic until May 10, 1973 when he again noted rectal bleeding. His hematocrit dropped to 29%. Once again the proctosigmoidoscopy and barium studies were negative. A liver-spleen scan revealed a central defect consistent with hematoma or cyst. He was then transferred to Walter Reed Army Medical Center.

In the past, diagnosis was rarely confirmed preoperatively and the physician had to rely mostly on clinical suspicion and exploratory laparotomy.

Physical examination was unremarkable except for a palpable non-tender splenic tip just below the left costal margin.

Initial laboratory studies revealed a hemoglobin of 11.7 gm%, blood urea nitrogen of 11 mg% and a normal urinalysis. The Monospot test was negative.

Protosigmoidoscopy was normal to a distance of 24 cm from the anal verge. The stools were negative for occult blood.

On the morning after admission he underwent Gamma-camera scanning of the abdomen 30 minutes after intravenous injection of 100 μCi/Kg. of ^{99m}technetium sodium pertechnetate. Potassium perchlorate was not administered to the patient. The scan revealed a focus of activity in the right lower quadrant distinct from the urinary bladder, an appearance similar to previously reported examples of Meckel's diverticulum located by this technique. (Fig. 1)

Elective surgery was planned to coincide with the summer holidays but was hastened by his third bleeding episode on June 1, 1973. At laparotomy a 3.5 or 2.0 x 1.5 cm Meckel's diverticulum 90 cm proximal to the ileo–cecal valve was identified and removed. An incidental appendectomy was performed and the enlarged spleen removed for diagnosis. It contained a 4.5 x 6 cm epidermoid cyst.

Discussion

The setting of recurrent rectal bleeding with negative proctosigmoidoscopy and barium radiography suggested the presence of a Meckel's diverticulum in this young patient. In

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medical annals of the district of columbia

vol. 42 no. 11 november 1973

the past, this diagnosis was rarely confirmed preoperatively and the physician had to rely mostly on clinical suspicion and exploratory laparotomy. Radiographic techniques[1] and laparoscopy[2] have been the only non surgical methods for diagnosis and their yield is unpredictable. ^{99m}Technetium sodium pertechnetate scanning of the abdomen was considered the next logical step in view of a few recent successful reports in the literature[3,4,5]. The result was rewarding and the diagnosis was established prior to surgery.

The possibility of false positives must be considered in every instance. Precautions such as fasting and nasogastric suction will eliminate the accumulation of gastric secretions in the proximal small bowel. Intravenous pyelography may be indicated to rule out partial ureteral obstruction or pyelectasis which could mimic this picture. Proper technique, accurate timing and emptying of the bladder are also required to avoid confusion with normal structures. Increased uptake by a hemangioma, an abdominal aneurysm or a peptic ulceration of the small bowel could at times be misleading. False positives by rectilinear scanning have also been reported in small bowel obstruction, small bowel intussusception and in abdominal abscess associated with ileal perforation[6,7].

Although fully aware of its limited indications, we feel that this rather simple, noninvasive technique has contributed greatly to the preoperative diagnosis of this entity, hitherto an extremely difficult task for the clinician.

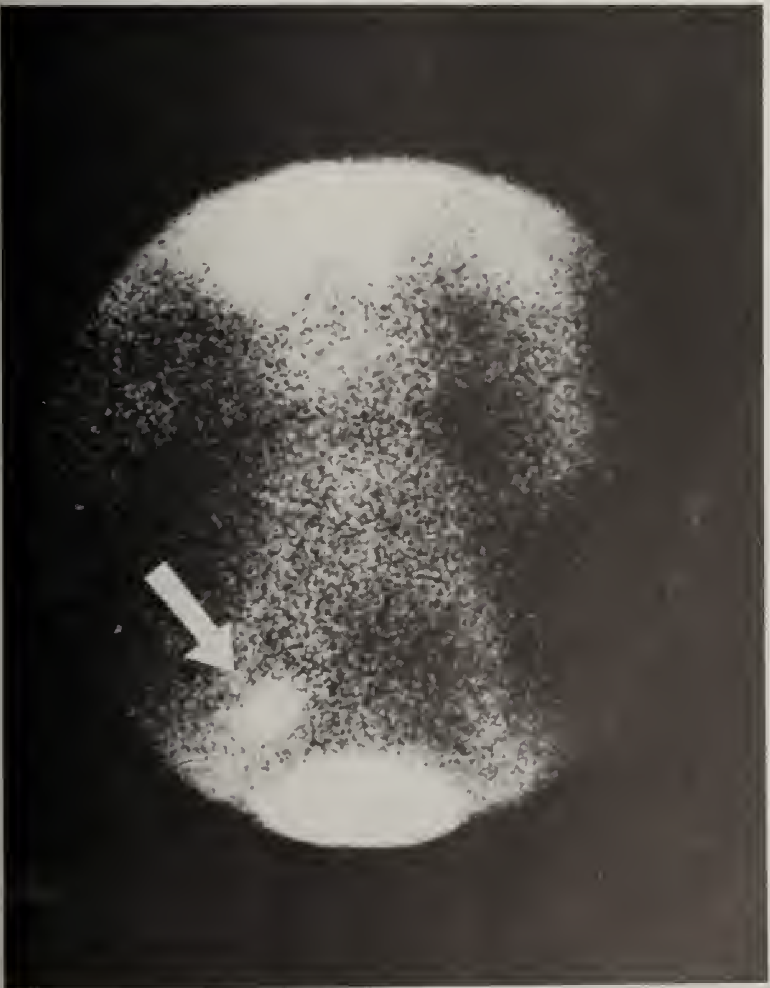

FIG. 1. Preoperative abdominal scan.

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THE VIEW BOX

(from page 552)

DIAGNOSIS: Cavernous hemangioma with extensive areas of sclerosis and thrombosis

Note in the lateral radiograph the mass which obliterates the base of the tongue and vallecula, displaces the epiglottis downward and has many round calcifications within it. Many of the calcifications have radiolucent centers and this suggests the Dx of hemangioma.

Hemangiomas in this area are uncommon. They often arise from the tonsillar capsule.

Angiography is helpful in outlining the vascular supply.

Edited by Gunter J. Augustin, M.D.
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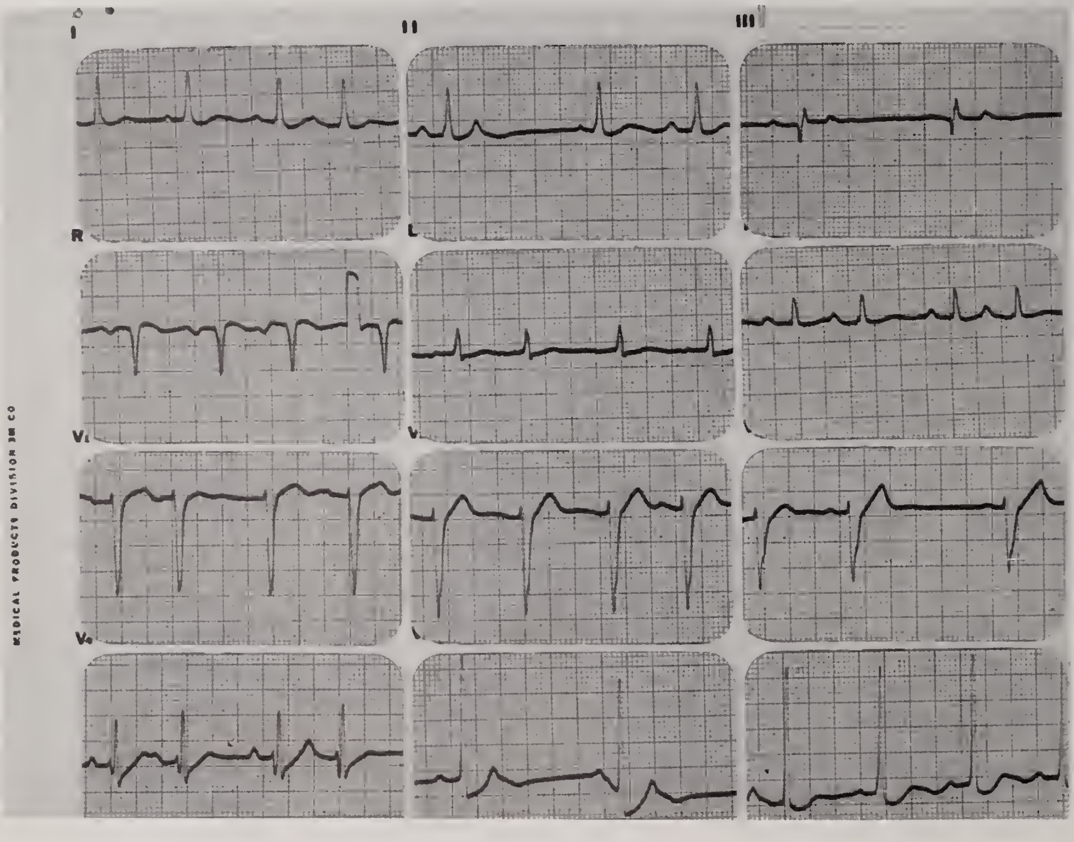
ECG Problems

HISTORY: Sixty-five-year old, white male with known coronary heart disease was admitted three days before this tracing was taken in acute congestive heart failure. The failure had responded satisfactorily to Digoxin, sodium restriction, and diuretics. Premature beats and skipped beats were noted on auscultation immediately preceding this electrocardiogram.

(For diagnosis see page 565)



Cardiorespiratory Complications of Intravenous Drug Abuse

RONALD R. BLANCK, MAJ., MC*, PETER T. SINGLETON, M.D.† and JULIUS L. BEDYNEK, COL., MC‡

Introduction

The epidemic of drug abuse seen in this country in recent years has resulted in many medical complications, particularly acute cardiorespiratory problems in young, previously healthy persons. Despite an apparent plateau of drug abuse, particularly heroin usage,[1] continued physician awareness of drug abuse-related complications is essential since prompt recognition and treatment of these complications is frequently life saving. Three cases seen recently at Walter Reed Army Medical Center illustrate cardiorespiratory aspects of this problem.

Case Reports

CASE #1. A 21 year old black male was seen in the Emergency Room with a history of dyspnea and intermittent unconsciousness for one hour. Friends related a history of drug abuse one year before, but denied knowledge of present use of drugs. The patient later admitted to current use of heroin. There was no history of cardiopulmonary disease. Physical examination revealed a young, thin, black male in a stuporous state. He responded poorly to questioning and was obviously dyspneic. His blood pressure was 158/90 with a regular pulse of 150/min. The pupils were constricted. There was no neck vein distension. Significant sternal retraction was noted. Coarse, moist rales were heard throughout both lung fields. The remainder of the examination, including the cardiovascular and neurologic systems, was normal except for peripheral cyanosis and a recent needle puncture in the left anticubital fossa. Portable chest x-ray on admission to the intensive care unit revealed bilateral hilar infiltrates suggesting pulmonary edema. The ECG showed peaked P waves with normal QRS axis, sinus tachycardia and prominent QRS voltage in the precordial leads. The initial arterial pO_2 was 26 mm Hg, the PCo_2 71 mm Hg and the pH 7.16. Treatment with nasal oxygen resulted in transient improvement; however, intubation was necessary 30 minutes after admission because of progressive cyanosis and hypoventilation. Following treatment with a narcotic antagonist, the patient improved slightly, but required maintenance on a pressure-regulated intermittent positive pressure respirator for 12 hours. Furosemide and sodium bicarbonate were also given intravenously. An ECG taken six hours after admission showed a shift in the frontal plane QRS axis to the right and +45 to +80 degrees, which, with the appearance of an rSR′ pattern in V1 and V2, suggested right heart strain. An ECG 12 hours later was normal. Repeat chest x-ray showed gradual clearing of the pulmonary edema and by 48 hours after admission the blood gases were normal. The patient improved until three days later when a right lower lobe bronchopneumonia appeared. This rapidly cleared with oral ampicillin and he was discharged on maintenance antibiotics. On follow up, recovery from heroin pulmonary edema with complicating bronchopneumonia was complete.

... convincing evidence for hypersensitivity, aspiration, and adulterant toxicity has been presented as the sole or major cause of pulmonary edema.

CASE #2. A 20 year old white male was seen with a history of cough, fever and chest pain for two days. The patient admitted regular intravenous heroin use for two years. Physical examination and chest x-ray at that time revealed a right lower lobe pneumonitis. He was initially treated with

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oral ampicillin, 500 mg every six hours. Four days later he began to complain of progressively severe precordial chest pain. Prostaphlin 500 mg every six hours and tetracycline 500 mg every six hours were added with no improvement. Two days later a three component pericardial friction rub was heard, and an electrocardiogram showed the elevated ST segment changes of acute pericarditis. Repeat chest x-ray at that time showed marked cardiomegaly and bilateral pleural effusion. He was admitted to the hospital where he was treated with oral prednisone, 10 mg every six hours, for one week. During this time his heart size returned to normal; he became afebrile and asymptomatic. The prednisone was discontinued but three days later the patient developed fever, spiking to 102°F. Shortly after, he was noted to have pulsus paradoxus of 20 mm Hg and jugular venous distension. X-ray revealed cardiomegaly, pulmonary venous congestion and left pleural effusion. Pericardiocentesis was performed that day with removal of 30 cc of thick bloody fluid and the patient was transferred to Walter Reed Army Medical Center. A repeat pericardiocentesis two days later was productive of 40 cc of similar appearing fluid. Cultures of the pericardial fluid and blood cultures were both positive for Pseudomonas aerugenosa sensitive to colimycin, which was administered 75 mg IM every eight hours. The antibiotic was discontinued after 18 days and the patient remained free of signs and symptoms of purulent pericarditis.

CASE #3. An 18 year old white male was seen because of headache, posterior neck pain, chest pain and fatigue for one day. He also complained of tenderness, swelling and erythema of the left forearm. He admitted regular use of intravenous propoxyphene hydrochloride and amphetamines for the previous six months. There had been chills and fever for the past four weeks. Two years before he had been evaluated for possible rheumatic fever and was placed on oral penicillin prophylaxis which was discontinued after one year.

Outpatient treatment was begun with oral ampicillin and penicillin, but symptoms persisted and the patient was admitted to the hospital three days later. Physical examination at that time revealed an oral temperature of 104°F. There was cellulitis of the left forearm about a recent needle puncture site and thrombophlebitis of the left calf. Also noted was a Grade III/VI systolic ejection murmur heard best over the apex with no diastolic murmur. The remainder of the examination was normal. Chest x-ray and ECG were within normal limits. Twelve blood cultures were sterile and a lumbar puncture was within normal limits. Ampicillin was continued until the third hospital day when the patient complained of a sharp substernal chest pain. A pericardial friction rub was heard for the first time and a Grade II/VI systolic ejection murmur was then heard best over the base of the heart. Intravenous staphcillin 1 gm every six hours and kanamycin 500 mg every six hours were begun. Cardiomegaly was then noted on x-ray. The patient's fever persisted. The patient was transferred to Walter Reed Army Medical Center where aqueous penicillin 4 million units intravenously every 6 hours was added. Three days later a Grade II/VI diastolic blowing murmur of aortic insufficiency was heard for the first time at the lower left sternal border and apex. The patient became afebrile one day later. The diastolic murmur persisted one more day; thereafter neither the diastolic murmur nor the fever was noted. The three antibiotic agents were continued for a total of six weeks during which time multiple repeat blood cultures were sterile. The heart size returned to normal and the patient was discharged without a specific pathogen ever recovered from blood cultures. One month later, examination was normal without evidence of residual infective endocarditis.

Discussion

HEROIN PULMONARY EDEMA

Opiate induced pulmonary edema was first described by Osler in 1880,[2] but only recently has it been appreciated how frequently this occurs. Suggested mechanisms include hypersensitivity (either immediate or delayed), neurogenic, hypoxic, direct toxic, aspiration, or adulterant toxicity reactions[3]. Heroin pulmonary edema occasionally occurs with the first mainline heroin experience, thus in those cases is unlikely to be a hypersensitivity reaction[4]. It is apparently not due to hypoxia induced left ventricular failure, since left ventricular filling pressures are normal on catheterizations. Also there is a higher protein content in heroin-induced pulmonary edema fluid than in cardiac failure edema fluid[5]. Furthermore, it is unlikely to be secondary to adulterant toxicity alone, since it occurs with methadone and morphine[6,2]. Most recent studies suggest hypoxia from respiratory depression as the main cause; direct drug toxicity may lead to increased capillary permeability, fluid extravasation, pulmonary hypertension and pulmonary edema itself, which further aggravates the hypoxia[5,3]. Heroin pulmonary edema has been compared to high altitude pulmonary edema with the following common findings: pulmonary hypertension due to anoxic pulmonary arteriolar constriction, normal or low pulmonary wedge pressures, no evidence of left ventricular failure, and no evidence of underlying cardiac disease[3,7].

Helpern described a syndrome of "acute narcotism" leading to rapid death in which pulmonary edema

A prolonged period of in-hospital high dose parenteral antibiotic therapy is mandatory once the diagnosis of ineffective endocarditis is made.

plays a central role. This syndrome was responsible for 48% of drug-related deaths between 1950 and 1961, and 80% of drug-related deaths from 1970 to 1971 in New York City[8,9]. It has been shown that with prompt recognition and treatment as outlined, mortality can be reduced to 18.3%[3].

In occasional cases, convincing evidence for hypersensitivity, aspiration, and adulterant toxicity has been presented as the sole or major cause of pulmonary edema[3,8,9,10]. Therefore, there may be multiple mechanisms involved.

Treatment is directed towards correcting hypoxia with intermittent positive pressure oxygenation or, if necessary, endotracheal intubation and oxygenation by respirator[11]. Narcotic antagonists such as naloxone hydrochloride should be used to neutralize any remaining narcotic. However, narcotic antagonists may precipitate an acute withdrawal reaction particularly in the absence of a depressed respiratory state[3]. Also, the antagonist may have a shorter duration of action than the narcotic, so that repeated doses of the antagonist may be required to prevent recurrence of the hypoxia. Antibiotics may be required, as there is frequently an associated bronchopneumonia. Steroid hormones, diuretics, and digoxin are generally of no value[11].

PURULENT PERICARDITIS

Purulent pericarditis has been recognized since the time of Galen[12] but is not known to the authors to have been previously reported as a complication of intravenous drug abuse. The disease is uncommon with a reported incidence of 0.67% in autopsy series[13]. Purulent pericarditis is most commonly associated with lung or pleural infections. Staphylococcus aureus and Diplococcus pneumoniae have been the two most common organisms found, with the incidence of staphylococcus increasing and pneumococcus decreasing since the advent of antibiotics[13,14]. Other bacteria and fungi must of course be considered, but are rare. The mortality rate in the pre-antibiotic era was over 50%, but since antibiotics the rate has been approximately 20%[14]. The classic features of purulent pericarditis as described in the pre-antibiotic era are modified and obscured by treatment of the pre-existing systemic or pulmonary infection with antibiotics[13]. Once initiated, pericardial infection may progress despite control of distant infection. There may be few recognizable clinical signs and the organism may not be cultured.

Therapy should be initiated with vigorous management including both antibiotics and closed pericardial drainage. If the patient does not rapidly improve, open drainage must be instituted and pericardiectomy is occasionally required[15]. Complications are relatively uncommon and consist of postpericarditis fluid retention and constrictive pericarditis[13].

INFECTIVE ENDOCARDITIS

Infective endocarditis is a common complication of intravenous drug abuse with 8.7% of addict deaths in New York City from 1950-1961 due to endocarditis and sepsis[8]. Other studies have shown a high mortality in patients with bacterial endocarditis from heroin abuse ranging from 38% to 79%[16,17,18]. However, a recent study has shown a mortality of less than 5%, attributed by the authors to prompt diagnosis and aggressive therapy[19].

Various studies have shown the left side of the heart to be involved most commonly, particularly with pre-existing valvular lesions; however, other studies have shown the right side to be involved most commonly[20,21]. Staphylococcus is the most frequently reported organism in right sided lesions[22,23]. Fungal infections are also more frequent in drug-abuse-associated endocarditis then in spontaneous endocarditis. Characteristically right sided endocarditis occurs on a previously normal valve, almost always the tricuspid, not the pulmonary. Septic pulmonary emboli are common. There may be few physical abnormalities with virtually no auscultatory findings. Left sided lesions characteristically involve previously normal or diseased valves, both mitral and aortic with streptococci, gram negative organisms, or fungi. Systemic emboli are common and physical signs are generally apparent, including auscultatory abnormalities[17].

Treatment is based on specific organism identification and antibiotic selection determined by careful bacteriologic sensitivity studies. Here, sophistication in the laboratory is essential, since the course of therapy depends on the continued sensitivity of the initially isolated and any superinfecting pathogens to serial dilutions of the patient's antibiotics containing serum. A prolonged period of in-hospital high dose parenteral antibiotic therapy is mandatory once the diagnosis of infective endocarditis is made.

Other pulmonary complications of intravenous drug abuse, in addition to heroin pulmonary edema, include pneumonitis, septic pulmonary emboli, pulmonary abscess, pulmonary fibrosis or granulomatosis (the so-called "mainliners lung"), and angiothrombotic pulmonary hypertension[17,19]. Cardiac lesions in addition to the infective endocarditis and pericarditis, may include myocardial infarction[24]. Vascular lesions include arterial occlusions, arterial emboli, mycotic aneurysms and thrombophlebitis[17,25].

Summary

This report describes three cases of cardiorespiratory complications of intravenous drug abuse seen at Walter Reed Army Medical Center. It is emphasized that prompt recognition and specific therapy resulted in improved survival with lessened morbidity. We believe that continued physician awareness is the most important pre-requisite to a favorable outcome in the treatment of these complications.

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Ineffective Erythropoiesis

ROBERT P. BROUILLARD, M.D., MAJ., MC*

Introduction

The concept and label *ineffective erythropoiesis* was first introduced in 1956 by Giblett, Finch, et al,[1] to designate a state wherein there is early destruction of red blood cells (RBC) and RBC precursors. This destruction takes place in the bone marrow or shortly after marrow release of the RBC. The concept has gained acceptance and is now essential to the understanding of the pathophysiology of certain anemias.

Topic Discussion

Erythropoiesis can be considered from a physiologic sense as being effective, ineffective or hypoproliferative[2] by considering the erythroid contents of the marrow and the peripheral reticulocyte count. In addition to proper interpretation of the marrow, the crude reticulocyte count is best considered in the fashion outlined by Hillman and Finch.[3] The crude reticulocyte count is a percentage dependent on the number of reticulocytes actually counted and the number of mature RBC's present. The crude reticulocyte count is therefore corrected as follows to obtain the absolute reticulocyte count:

The corrected reticulocyte count is low in the face of a moderate to severe anemia and the marrow is cellular with an increase in the percentage of RBC precursors.

$$\text{Absolute Reticulocyte Count} = \frac{\text{Observed Hematocrit}}{\text{Predicted Hematocrit}}$$

This number may be expressed as a percentage or as an absolute number of reticulocytes per mm^3.

A second correction is necessary because of the demonstration that erythropoietin causes early release of the reticulocyte from the marrow, and thus its life span in the peripheral blood is prolonged increasing the reticulocyte count[4]. With a hematocrit of 45%, the reticulocyte can be expected to survive one day and as the hematocrit falls its survival is extended (See Table).

HEMATOCRIT	LIFE SPAN (DAYS)
45	1.0
35	1.5
25	2.0
15	2.5

This so called shift reticulocyte correction is applied to give the corrected reticulocyte count.

$$\text{Absolute Reticulocyte Count} = \frac{\text{Corrected Reticulocyte Count}}{\text{Life Span}}$$

The corrected reticulocyte count allows evaluation of the adequacy of the marrow response to a given level of anemia. Under maximal stress the marrow should increase RBC production by a factor of at least three (corrected reticulocyte count of three or greater). A corrected reticulocyte count of less than three under these circumstances implies a defect in erythropoiesis. An adequate count in the face of a low hematocrit defines effective erythropoiesis. This is the situation usually seen in an uncomplicated hemolytic anemia.

The term hypoproliferative erythropoiesis is applied when there is a lack of iron or an intrinsic marrow abnormality such as a toxic insult or defect in the microenvironment which leads to a quantitatively deficient marrow response. In these conditions, with the exception of iron deficiency, there is often little abnormality of the peripheral RBC morphology, the bilirubin and lactate dehydrogenase (LDH) are normal and the marrow shows erythroid hypoplasia. Hypoproliferative anemias also occur in the face of decreased erythropoietin levels as is the case in severe renal disease.

Ineffective erythropoiesis is distinguished from the hypoproliferative anemias by its quantitatively abnormal response. This abnormal response in most cases is a maturation defect and is best illustrated by the megaloblastic anemias. The corrected reticulocyte count is low in the face of a moderate to severe anemia and the marrow is cellular with an increase in the percentage of RBC precursors. The explanation for this seeming paradox was provided by studies with ^{15}N labeled glycine[5].

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Glycine is a precursor of heme and it was expected that the administered label would appear as fecal urobilinogen 120 days after administration corresponding to the RBC life span. However, in addition to the expected appearance at 120 days there was an "early labeled peak" at three to five days. This has subsequently been shown to be due to intramedullary destruction of developing RBC precursors. In megaloblastic anemias there is a striking increase in the "early labeled" bilirubin peak[6]. There are several possible etiologies for this intramedullary cell destruction: A) increased phagocytic activity by marrow histiocytes shown by electron microscopy ingesting megaloblasts[7]; B) megaloblasts are more susceptible to autohemolysis than normal cells[8]; C) a fraction of defective hemoglobin or excess globin chains may be expelled from immature RBC[9]; D) defective young cells may be sequestered by the peripheral RES almost immediately upon release from the marrow[10], and finally; E) recent evidence[11] suggests that the porosity of the marrow sinusoidal wall is limited in such a way as to allow only mature and therefore pliable RBC's to escape to the periphery.

Ineffective erythropoiesis is prominent in all megaloblastic states whether due to B$_{12}$ or folate deficiency, drugs or unknown causes as in the unresponsive megaloblastic states. It also occurs in many hemoglobinopathies particularly thalassemia where, as suggested above, pitting of excess chains from the cells results in intramedullary loss of hemoglobin. Other miscellaneous states such as Heinz body anemias and idiopathic refractory sideroblastic anemia[12] have a component of ineffective erythropoiesis.

Diagnosis and quantitation of ineffective erythropoiesis can be somewhat cumbersome but a clue to its severity can be gained from the level of the RBC LDH isoenzyme. In the megaloblastic states it is higher than would be expected in a peripheral hemolytic anemia due to the higher concentrations of LDH in immature and megaloblastic RBC precursors[13,14]. A more direct approach is the use of ^{59}Fe to study ferrokinetics. Patients with ineffective erythropoiesis have an increased plasma iron turnover but a decreased incorporation of administered radioactive iron into circulating RBC[15]. Increased plasma iron turnover is associated with either increased turnover of iron stores or ineffective erythropoiesis. As iron stores can not turnover at the rate seen, the increased plasma turnover is therefore due to ineffective erythropoiesis.

Endogenous carbon monoxide (CO) production measurement is an accurate method to quantitate ineffective erythropoiesis.[16,17] This technique is based on the release of one mole of CO for each mole of heme converted to biliveredin under the influence of microsomal heme oxygenase. By enclosing the patient in a closed rebreathing system the increment in carboxyhemoglobin percent saturation can be measured and provides a method for obtaining serial CO production rates in a patient. The advantage of this technique is that it can be repeated at will whereas isotopic methods are limited by radiation dose. Endogenous CO measurement would appear to be an ideal method to study the early effect of therapy in conditions such as refractory megaloblastic and sideroblastic anemias.

Summary

The foregoing discussion illustrates the value of an approach to anemia based on an evaluation of the effectiveness of erythropoiesis. This requires determination of the corrected reticulocyte count and knowledge of the size of the marrow erythroid compartment. If the corrected reticulocyte count is inappropriately low and erythroid marrow precursors are plentiful, erythropoesis is ineffective and measurement of endogenous CO production provides a valuable tool for study of this condition.

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ECG Diagnosis

(from page 558)

INTERPRETATION:
1. Frequent atrial premature beats, some not conducted.
2. Left ventricular hypertrophy.
3. Old myocardial scarring.
4. ST-T changes probably reflecting digitalis effect and myocardial ischemia.

The patient has apparently not had an acute myocardial infarction. The rhythm shows interesting combinations of atrial premature beats and relatively long pauses. The pauses, seen following the first beat in lead II, both beats in lead III, the second beat in lead V_3, and both beats in lead V_5, were interpreted as representing sinus arrest or SA block ("sinus pause"). However, the T wave preceding each of these pauses is distorted. This shows clearly in the first beat in lead II. That T wave is peaked, giving it quite a different contour from the T wave following the next beat. This strongly suggests that a P wave is superimposed upon that T wave. The same observation can be made concerning each of the T waves preceding a long pause. These superimposed P waves represent the atrial complexes of very early atrial premature beats. The ventricles are still refractory from the preceding beat, hence the atrial premature beat is not conducted to the ventricles. The mechanism underlying these premature beats is probably the same as that which causes all the other atrial premature beats in this electrocardiogram, the only difference being that these beats are a little more premature.

In this case, the ectopic activity ceased when the digitalis dose was decreased. They were apparently the result of slight digitalis toxicity.

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SPECIAL ARTICLE

New Concepts in Asthma

HYMAN M. KAPLAN, M.D.* AND GEORGE W. WARD, JR., M.D.†

If there is a defect in the parasympathetic reflex, would atropine be of use in preventing or treating asthma?

Asthma is one of the more frequent medical problems facing the physician and is not an infrequent cause of death.[1,2] Inhalant antigens, respiratory infections, physical, chemical and psyche stimuli may lead to asthma but there are three resulting pathological findings: (1) bronchospasm, (2) accumulation of secretions, and (3) mucosal edema. More recent advances in the understanding and treatment of asthma have been based on cellular and physiological theories that attempt to explain these findings in the asthmatic patient.

The peripheral autonomic nervous system[3] is anatomically and functionally divided into the parasympathetic (cholinergic) and sympathetic (adrenergic) divisions (Table 1). Based on responses of end-organs to sympathomimetic stimulating and blocking agents the adrenergic division was postulated to have two receptors: an alpha receptor and a beta receptor.[4] The beta receptor could be further divided based on the following responses: Beta$_1$ gives increased free-fatty-acids (FFA) and cardiac stimulation and beta$_2$ stimulation results in bronchial relaxation and vasodilatation[5].

Based on these concepts the motor innervation of the tracheobronchial tree is diagrammed in figure 1. The parasympathetic preganglionic fibers synapse near the tracheobrobronchial tree and give rise to short postganglionic fibers. The activity of this cholinergic innervation is smooth muscle contraction causing bronchoconstriction[6]. Bronchial challenge with agents including carbon dust, sulphur dioxide, antigens, cold air, histamine or cholinergic agents will increase airway resistance in asthmatic subjects[6-13]. These responses can be blocked by premedication with atropine. Direct stimulation and blockade of vagal activity in animals have further substantiated the role of the parasympathetic motor division in bronchoconstriction[13-15].

The afferent or sensory innervation has not been studied as extensively as the motor system but subepithelial receptors[6,7] have been found to extend from the larynx to the respiratory bronchioles and it is believed that

TABLE 1

PERIPHERAL AUTONOMIC MOTOR SYSTEM

I Parasympathetic (Cholinergic)

II Sympathetic (Adrenergic)
- A. Alpha receptors
- B. Beta receptors
  - 1. Beta$_1$ receptor (Cardiac stimulation/Lipolysis)
  - 2. Beta$_2$ receptor (Bronchodilation/vasodilation)

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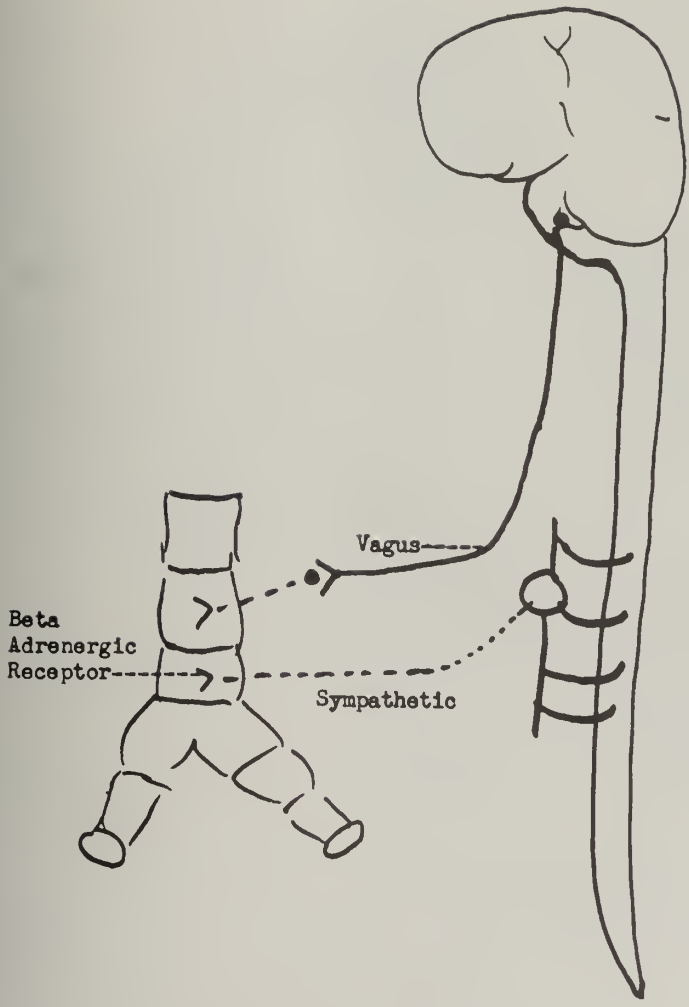

FIG. 1. Innervation of the Tracheobronchial Tree.

they are conducted back to the central nervous system primarily by way of the vagus nerve[16]. These receptors mediate the cough reflex and may play a role in reflex bronchospasm[7].

The sympathetic outflow originates in the spinal cord from the first through fourth thoracic interspaces (figure 1). These short preganglionics synapse in the stellate ganglion and send sympathetic fibers to the tracheobronchial tree. These sympathetic receptors in the tracheobronchial tree are thought to give primarily a beta adrenergic response[6] and more specifically a beta_2 or bronchial relaxation response[5].

Important concepts and theories of the beta adrenergic receptor at the cellular level have been advanced since the discovery of Cyclic AMP (CAMP) as an intracellular messenger[17]. Figure 2 represents this important intracellular theory: Adenyl cyclase is thought to be the beta adrenergic receptor and the enzyme catalyzing the conversion of adenosine triphosphate (ATP) to CAMP. CAMP acting as an intracellular messenger may mediate many hormonal activities and importantly, bronchial smooth muscle relaxation and also histamine release inhibition. CAMP is metabolized to 5-AMP by the action of phosphodiesterase. Two classes of agents, catecholamines (including endogenously produced or exogenous medication) and methylxanthines (aminophylline or theophylline), increase the level of CAMP by stimulating adenyl cyclase or blocking phosphodiesterase activity respectively. This may be important in clinical considerations in that aminophylline may be effective in the epinephrine resistant asthma attack. Cromoyln sodium has not been shown to effect this CAMP system[18] and the ability of this drug to prevent exacerbations of asthma has not been explained although it is thought to block the release of mediators from the mast cell. The precise role that steroids play in this CAMP system is not known. However, *in vitro* studies have shown steroids will restore the responsiveness of lymphocytes (taken from asthmatic patients) to release normal amounts of CAMP upon stimulation with catecholamines, such as isoproterenol[19].

Applying these concepts in the search of the etiology of asthma gives rise to several theories or mechanisms as follows: (1) In antigen induced asthma, IgE dependent mediator release may have direct effects on the bronchial smooth muscle or act via parasympathetic sensory receptors, (2) Tonic bronchoconstriction via the parasympathetics may be constantly increased in activity or the supepithelial (cough) receptors may respond at a lower threshold on stimulation, (3) The beta adrenergic receptor may not respond (beta adrenergic blockade[20]) with normal bronchodilator activity or (4) endogenous catecholamines may be decreased.

These theories have produced interesting questions when applied to clinical situations. Does the atopic patient manifest his allergies as asthma due to one or more of these postulated mechanisms? If there is a defect in the parasympathetic reflex, would atropine be of use in preventing or treating asthma? Does paradoxical asthma following isoproterenol aerosols result from the metabolism of this catecholamine to a beta blocking agent[21,22]? Can catecholamines overcome beta blockade[23]? These questions have been reviewed elsewhere[24-26] and have provoked many interesting clinical and laboratory studies.

Although the theoretical concepts and clinical correlations have not been entirely proven, the known data may provide a practical approach to the therapy of asthmatic patients. Not only should inciting factors be investigated and avoided or treated, but a therapeutic regimen giving effective bronchodilatation is obviously of utmost importance. Round-the-clock regimens of bronchodilators such as aminophylline and ephedrine or isoproterenol to increase intracellular levels of CAMP certainly appear therapeutically indicated. Occasionally the unresponsive or difficult to manage patient will necessitate the use of steroids and/or cromolyn sodium. A careful and well planned approach to each individual patient will most often give gratifying therapeutic results.

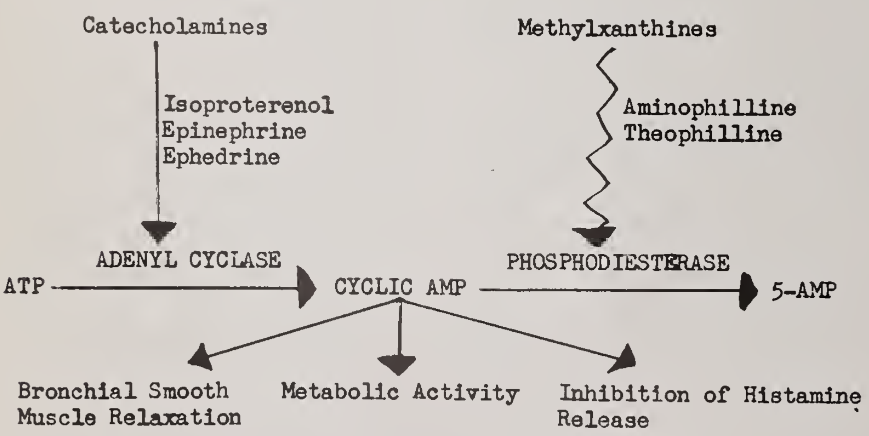

FIG. 2. Beta Adrenergic Receptor.

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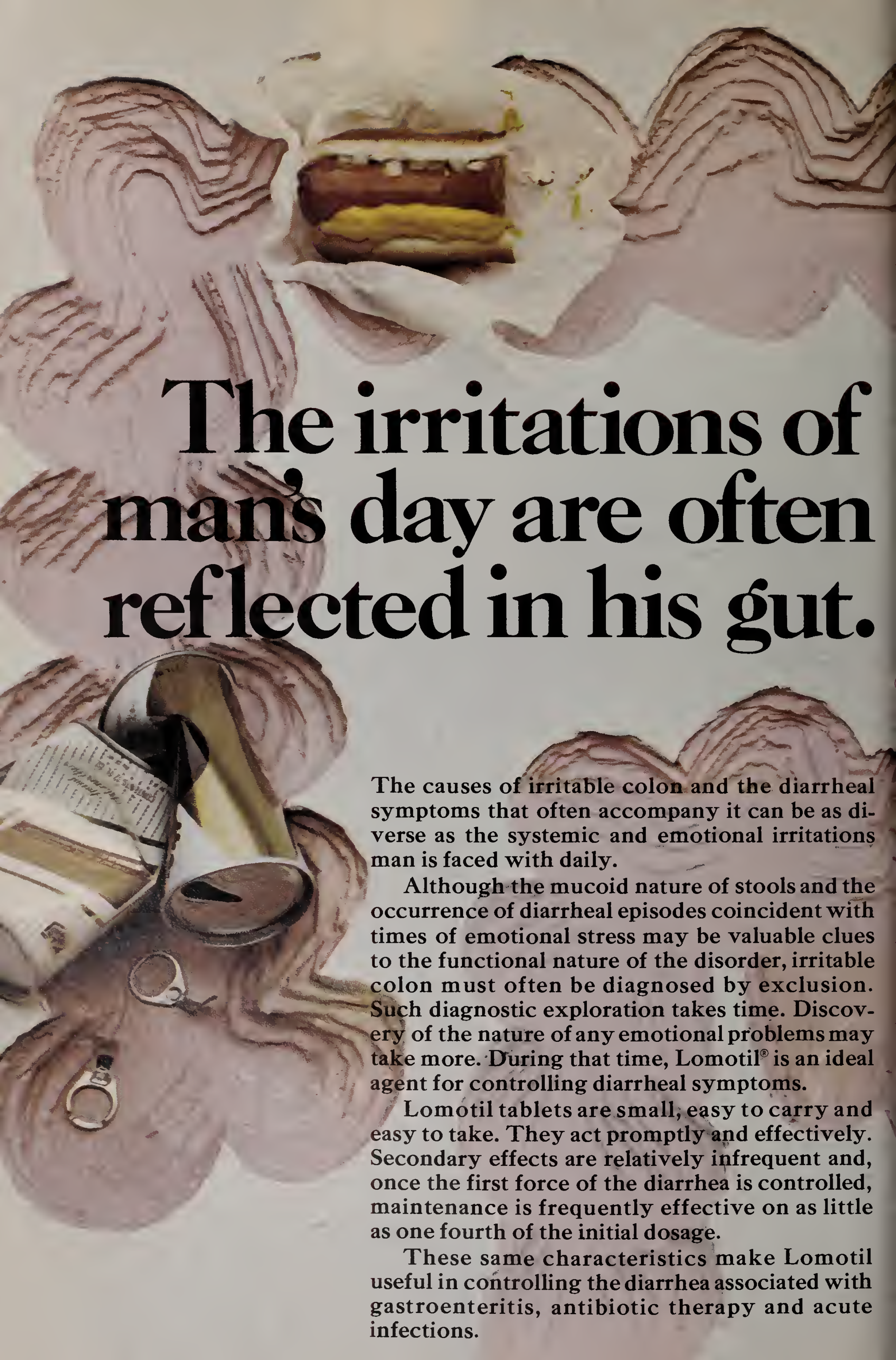

The irritations of man's day are often reflected in his gut.

The causes of irritable colon and the diarrheal symptoms that often accompany it can be as diverse as the systemic and emotional irritations man is faced with daily.

Although the mucoid nature of stools and the occurrence of diarrheal episodes coincident with times of emotional stress may be valuable clues to the functional nature of the disorder, irritable colon must often be diagnosed by exclusion. Such diagnostic exploration takes time. Discovery of the nature of any emotional problems may take more. During that time, Lomotil® is an ideal agent for controlling diarrheal symptoms.

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IMPORTANT INFORMATION: This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

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INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

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If a complete history and examination rule out allergic rhinitis, the long-term outlook will be a lot more favorable than his own "diagnosis" would have indicated.

But right now, whether he's got allergic rhinitis or a cold, he's suffering from the same irritating symptoms of drip, congestion and stuffiness. Try DIMETAPP EXTENTABS®. They're formulated to relieve these symptoms without much chance of causing drowsiness or overstimulation. Your patients will appreciate the 24-hour relief they can get from just one tablet every 12 hours.

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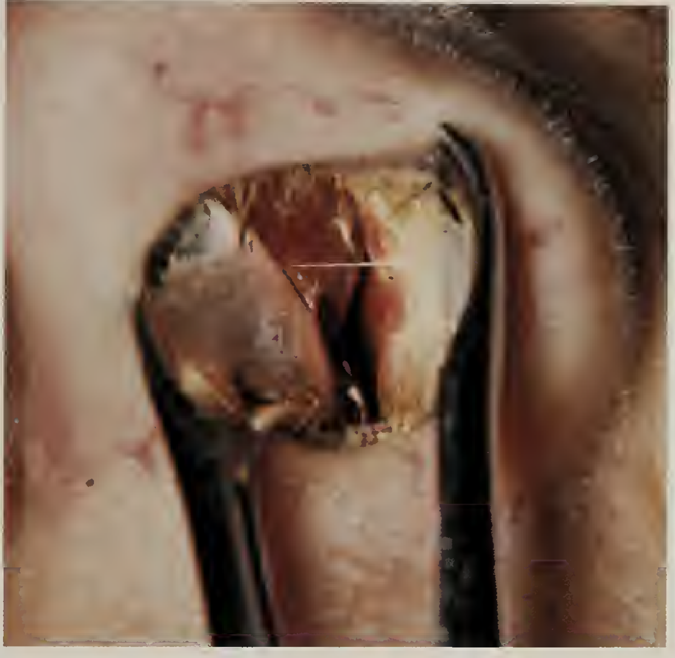

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Whether it's a cold or an allergy, Dimetapp Extentabs® effectively relieve stuffiness, drip and congestion.

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CONTRAINDICATIONS: Hypersensitivity to antihistamines of the same chemical class. Dimetapp Extentabs are contraindicated during pregnancy and in children under 12 years of age. Because of its drying and thickening effect on the lower respiratory secretions, Dimetapp is not recommended in the treatment of bronchial asthma. Also, Dimetapp Extentabs are contraindicated in concurrent MAO inhibitor therapy.

WARNINGS: *Use in children:* In infants and children particularly, antihistamines in overdosage may produce convulsions and death.

PRECAUTIONS: Administer with care to patients with cardiac or peripheral vascular diseases or hypertension. Until the patient's response has been determined he should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc. Patients receiving antihistamines should be warned against possible additive effects with CNS depressants such as alcohol, hypnotics, sedatives, tranquilizers, etc.

ADVERSE REACTIONS: Adverse reactions to Dimetapp Extentabs may include hypersensitivity reactions such as rash, urticaria, leukopenia, agranulocytosis and thrombocytopenia; drowsiness, lassitude, giddiness, dryness of the mucous membranes, tightness of the chest, thickening of bronchial secretions, urinary frequency and dysuria, palpitation, hypotension/hypertension, headache, faintness, dizziness, tinnitus, incoordination, visual disturbances, mydriasis, CNS-depressant and (less often) stimulant effect, anorexia, nausea, vomiting, diarrhea, constipation, and epigastric distress.

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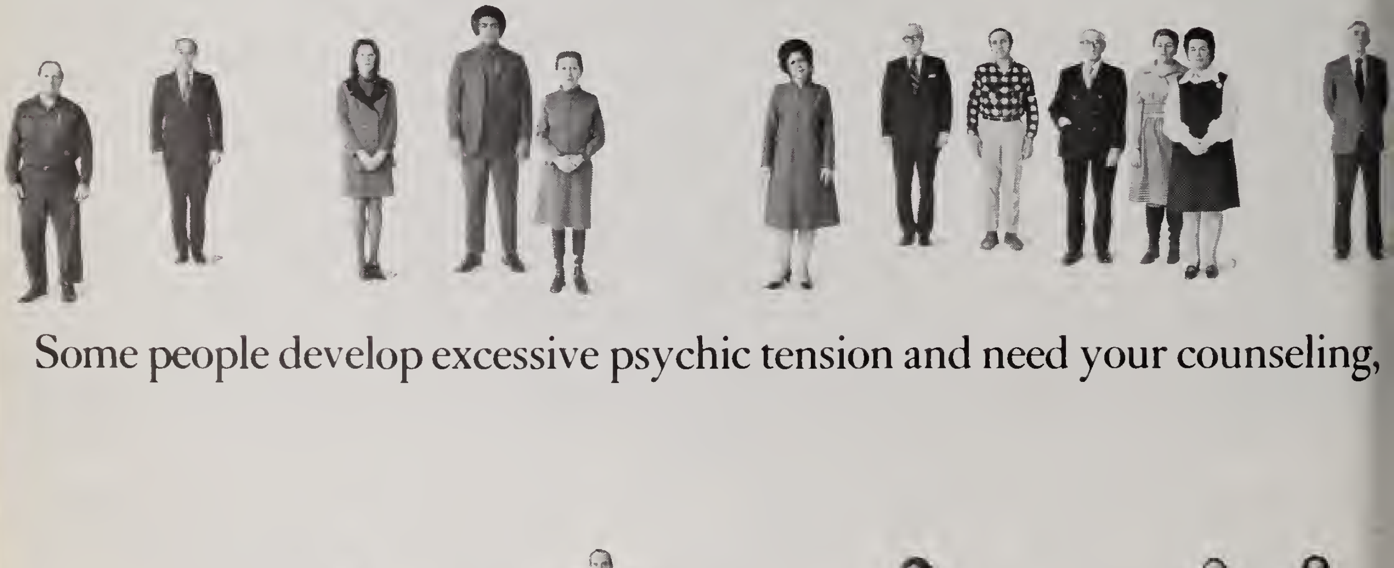

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While Valium can be a most helpful adjunct to your counseling, it should be prescribed only as long as excessive psychic tension persists and should be discontinued when you decide it has accomplished its therapeutic task. In general, when dosage guidelines are followed, Valium is well tolerated (see Dosage). For convenience it is available in 2-mg, 5-mg and 10-mg tablets.

Drowsiness, fatigue and ataxia have been the most commonly reported side effects.

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Before prescribing, please consult complete product information, a summary of which follows:

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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COMMITTEE ON ADOLESCENCE AND PREADOLESCENCE

Appropriate Attitudes & Values

The Committee on Adolescence and Preadolescence was created on January 15, 1972, because there was a need for the profession to become more acutely aware of the complex problems confronted by this important age segment of the District's predominantly black population. Many of the adolescent problems are contributed to an inappropriate value structure. It was felt that, if preadolescent attitudes could be accurately isolated and understood, a more comprehensive program of teaching appropriate values to preadolescents could be developed. Six or seven educatable attitudes were chosen by the Committee and were discussed on March 27 at a Committee meeting.

It became apparent that in order to begin teaching eight to twelve year olds various value-related attitudes, it would be necessary to alert parents prior to the teaching event. The philosophy of teaching attitudes toward death, sexology, or parent-child relationships for example, sees history repeating itself in a spiral manner.

The teaching of a preadolescent, at a very crucial stage in the development, might be discontinued by the parent. Therefore, a program would include the public schools. The educators and psychologists of the office of education or school system would help develop the program details. If the program is approved by the government, a pilot project could be recommended in several communities to determine how effectively this program would function. A teacher or nurse, who studied the program's materials, would then work with the children and the parents.

There is no better period of time to teach attitudes than in this preadolescent period. While it would be ideal to teach at an earlier age, teaching is best at age seven or eight and then continues for a few years after which the attention span on attitudes and teachable attitudes is lost. The optimum age, therefore, is seven or eight. This is somewhat similar to the optimum age in teaching physical skills and sports, such as swimming or swinging a golf club. Studies have proven that there are "best ages" to learn to swim at age five than at age twelve, and the accomplishment is always more successful.

Our Committee feels that teaching appropriate attitudes is necessary for the successful and happy development of the adolescent. Representatives of the H.E.W. told the Committee that a study of this kind has not been done before. We have had guest advisors from the Department of Health Education and Welfare and the D.C. School System. Also a curriculum educator from the Montgomery County Schools spoke to the Committee.

Obviously, this is a program idealistically oriented but should be interesting to the pragmatic Medical Society. We must get the data we have in mind through proper channels and hopefully useful information can reach the child. This is a very difficult problem and we are all aware that it may take some time before this can be accomplished. Meanwhile, the Committee will continue in its effort. For the Medical Society of D.C., it is an excellent public relations effort.

Ultimately, the major effort will be transferred from the Medical Society group to the educators and psychologists. We will then remain in an advisory role and continue to feed impetus into the program.

Recently the Executive Board of the Medical Society approved the resolution that "a program on sex education be offered in the school curriculum for junior and senior high school students. The Society would be agreeable to helping in any way that the educators would suggest." As a result of this action by the Board, a letter was sent to the Director of the Department of Health and Safety, D.C. Public Schools, offering assistance by the Committee on Adolescence and Preadolescence. This was accepted by the Director, Mr. Frank Bolden, who has now accepted an invitation to serve on our Committee.

WILLIAM LEWIS, M.D.
Chairman
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book REVIEWS

Progress in Liver Diseases, Vol. 4. H. POPPER AND F. SCHAFFNER, Editors. Price, $29.75. Pp. 640 with illustrations. New York: Grune & Stratton, 1972.

This volume of PROGRESS IN LIVER DISEASES more than equals past editions in quality and scope. Thirty-five excellent reviews present the most recent data relating to such diverse topics as the nature of Australia antigen, the treatment of chronic hepatitis, and the photochemical and biochemical basis of the treatment of neonatal jaundice.

The book should appeal to both basic scientist and clinician. Well referenced, up-to-date sections on lipoproteins and the liver, the physiology of bile flow, and the microsomal biotransformation system in cholestasis will interest some. Others will be attentive to chapters on renal failure in advanced liver disease, alcoholic hepatitis, and hepatic drug reactions. These and other chapters such as those on hepatic coma and the management of ascites provide both the latest pathogenetic data as well as rational therapeutic suggestions.

Although some recurrent themes such as hepatic carcinogenesis and hepatitis virology have appeared in earlier editions, there is litte repetition. Different avenues of approach and exciting new data make these sections particularly interesting. The section devoted to ethanol metabolism perhaps deserves special note. The three enzymatic pathways for ethanol metabolism are carefully explained. Then the challenging controversies as to the relative roles of each pathway are presented in an exciting and cogent fashion by authors actively engaged in the scientific disputes.

Volume IV is the current state of the art. It is a must for those who wish to keep abreast of the advances being made in the study of liver diseases.

ALLEN L. GINSBERG, M.D.

Hemodialysis. Principles and Practice. GEORGE L. BAILEY, M.D., Editor. Price, $24.50. Pp. 496. New York: Academic Press, 1972.

This book is largely a collection of papers presented at the 1970 Meeting of the Association for the Advancement of Medical Instrumentation. Some additional chapters are included in a fairly successful attempt to present a complete practical text on hemodialysis.

The chapters on uremia as a total-body disease, pharmacodynamics in renal failure, and complications of treatment with dialysis would be of interest to most physicians and students. They are informative and easily readable and offer quite lengthy bibliographies for those whose special interest is nephrology.

The remainder of the book would be of interest mainly to physicians, nurses, and paramedical personnel who are directly involved in hemodialysis. It includes sections on diet therapy, physical principles in hemodialysis, circulatory access, psycho-social aspects, and characteristics of coil, parallel flow, and capillary hemodialyzer systems. All of these are quite clear and well-written. However, one cannot help but question the usefulness of devoting 82 pages of the text to step-by-step directions for assembling and operating the twin coil and Kiil dialyzers. It would seem that most people involved in dialysis would already have developed similar outlines for use in their units.

In summary, this book is quite a useful addition to the dialysis literature, offering good coverage of a wide number of topics.

ANNE M. THOMPSON, M.D.

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Physiology, Emotion & Psychosomatic Illness. A CIBA FOUNDATION SYMPOSIUM 8 BOOK. Price, 18.75. Pp. 421 with illustrations. New York: American Elsevier Co., 1972.

This book reports the proceedings of the Symposium on Physiology, Emotion and Psychosomatic Illness held at the Ciba Foundation, London, 18th-20th April 1972.

A total of 26 participants and 17 papers were presented. In addition, there is an introduction and a summary by the Chairman, Sir Dennis Hill. Each paper is followed by a discussion. The papers deal with the concept of emotions, the physiological elements involved in the expression of emotions and the anatomical substrates of emotions. Finally there is a discussion of the application of these principles to psychosomatic illnesses.

The papers in this book are quite scholarly and are written by experts in the field who are reporting the results of their research. Since all the papers represent original work, one finds it difficult to be critical. The book is interesting and stimulating but not the type of book that belongs in a clinician's library. It should, however, prove to be profitable reading to those who are doing research in the field of Psychosomatic Illness.

MORRIS KLEINERMAN, M.D.

Photomicrography. DOUGLAS LAWSON. Price, $21.50. Pp. 494 with illustrations. New York, Academic Press, 1972.

The purpose of this book is to create a better understanding of the working principles involved in the production of a picture through the microscope. The reason this objective will likely be achieved is the thoroughness and comprehensive nature of the subject matter which is presented in a concise manner. A unique feature is the replacement of chapters with subject headings, nearly 80 of them, that cover in readable style the construction of microscope lenses, their image-forming qualities, the structure and uses of simple and compound microscopes, the many aspects of plain and special lighting, the use of filters, the various techniques of photomicrography, the requirements of film processing, esthetic considerations, and an extensive treatise on cinemicrography. There is a useful section on the faults of photomicrography. The wide scope of this subject matter is supported by over 270 line drawings and many pictures of photographic equipment.

The 355 pages of text are followed by 130 pages of plates, 22 in full color, that are attended by generous and often full-page captions. The index is extensive. The printing is somewhat small but this is more than made up for by the scope of the abundantly illustrated work and the practical nature of the information provided. While useful to physicians, the book is a guide to all interested in photomicrography.

CHANDLER SMITH, M.D.

The Management of Neonates and Infants with Congenital Heart Disease. DONAL M. BILLIG, M.D. AND MARSHALL B. KREIDBERG, M.D. Price, $12.75. Pp. 182. New York, New York: Grune and Stratton, 1973.

This is indeed a different book from the usual text on congenital heart disease as the author indicates in the preface. The chapters are short, succinct and informative. The 3 major central shunts and the important right and left heart lesions as well as the more common causes of cyanotic heart disease are covered. The book's major contribution lies in the section on surgical approach and treatment of these various conditions. In this era of increasing pressure for immediate total correction, the authors add a refreshing broader look. The efficacy of old standby palliative procedures such as pulmonary artery banding, atrial septostomy, Blalock-Hanlon procedure, etc. is given consideration.

The cardiologist and pediatrician who have to deal with the problem of congenital heart disease will find this book a very useful source of information on the current status of management. Knowledge of the results from the various modes of surgical intervention should be invaluable in helping guide decision making toward the patient's best interest.

ANTONIO C. deLEON, JR., M.D.

medical annals of the district of columbia

vol. 42 no. 11 November 1973

Auxiliaries in Health Care. N. R. E. FENDALL. Price, $9.00. Pp. 200. Baltimore, Maryland: The Johns Hopkins Press, 1972.

No one can disagree that the health care needs of people in the developing world cannot be met by physicians alone. As the author states in his conclusion, "There is no hope of rendering adequate medical care to all of those in need without auxiliary personnel."

Dr. Fendall is a former director of medical services in Kenya, where he developed and led programs for the training and deployment of medical auxiliaries. In this book, he enumerates the possibilities for the training and successful utilization of auxiliaries in health care delivery, family planning, maternal and child health care, environmental health, medical technology, pharmacy, and dental care. Specific examples, further illustrated by numerous well-placed tables, are given on the needs for auxiliaries and how these are being met in such countries as Jamaica, Guatemala, Thailand, Senegal, Nigeria, and Kenya.

The material covered is only broadly applicable to those in this country involved in such programs as the training and utilization of Physician's Assistants. The book is admittedly offered to assist those closely involved with creating more extensive health programs in the developing world. I would agree with the author that rather than needing to read the entire book, the reader should peruse the opening chapters to obtain an understanding of the author's valuable outlook and definitions; turn to the chapter related to the readers specific discipline; and finally read the last chapter which outlines Dr. Fendall's concepts and principles. This is a well-written book on an important and topical subject and the author is to be congratulated for his complete and lucid presentation.

MARTIN S. WOLFE, M.D.

Vectorcardiography. ALBERTO BENCHIMOL, M.D. Price, $18.50. Pp. 223 with illustrations. Baltimore, Maryland: The Williams & Wilkins Company, 1973.

Dr. Benchimol's contribution to the book shelf on Vectorcardiography represents a personal summary of a large experience in the field. His intent is illustrative rather than comprehensive, although he devotes brief necessary chapters to reviewing lead systems and describing the anatomic and electrical correlation of myocardial activation. Subsequent chapters cover selected diagnostic entities, including atrial and ventricular hypertrophy, conduction defects with special attention to hemiblocks, myocardial infarction and injury, arrhythmias, and pre-excitation. The book is relatively small and well illustrated, although the text and illustrations tend to stand independently rather than being complimentary. The book would serve as a reasonable introduction to those unfamiliar with vectorcardiograms, but it lacks the documentation or erudition necessary to stand as a summary or review of the field.

The chapters on myocardial hypertrophy make only a token effort at objective quantitation. Quantitation assumes importance in vectorcardiography to develop more exacting criteria which would justify the use of the vectorcardiogram above and beyond the standard electrocardiogram. Dr. Benchimol uses control data based only on his own fifty normal studies without reference to data from the literature. No effort is made to emphasize the overlap between normals and controls. Emphasis is placed on qualitative recognition of vector loops without mention of the orthogonal tracings available with the vectorcardiogram.

The text of the book is interspersed with "clinical pearls" such as mortality associated with surgical replacement of the aortic valve when left anterior hemiblock accompanies aortic stenosis. Once again, documentation or references are lacking. Such clinical awareness adds readibility and interest, but one wishes the author had instead offered some new insights into clinical vectorcardiographic dilemmas such as differentiating posterior infarction from type B RVH or the five to ten percent of normal people with similar VCG finding of an anterior displaced horizontal loop.

A substantial chapter describes the technique of "Timed Vectorcardiography". This technique represents a running record of the vectorcardiography loops on a strip recorder, in contrast to the isolated "still" loop. The records produce temporal separation of atrial, as well as ventricular depolarization and repolarization loops; the E point or baseline is well defined by the line between loops. In this chapter the text consists of a primer of basic arrhythmias. One is left with the impression that this technique is the author's personal vindication of the vectorcardiogram as a tool to demonstrate arrhythmias. However, no case is made for the advantage of this elaborate technique over standard electrocardiographic or orthogonal lead strips. The definition of depolarization in aberrant conduction associated with arrhythmias may be one useful byproduct. The author also intersperses His bundle recordings with the timed vectorcardiograms, adding to the sophistication of his discussion of arrhythmias, but detracting and confusing the neophyte who is concentrating on learning vectorcardiography.

The final chapter consists of examples of vectorcardiograms and corresponding electrocardiograms in specific disease states, presumably to summarize the lessons of the book. Unfortunately, the selection of cases seems unnecessarily atypical and esoteric. One case of Ebstein's anomaly is illustrated without the conduction disturbance most typical of that lesion. Two of the nine illustrations are variations of corrected transposition of the great vessels, and a case of mitral valve prolapse is illustrated with left anterior hemiblock, which does not typify that entity.

In the book *Vectorcardiography,* Dr. Benchimol has done what a lecturer might attempt in presenting new materials to an inexperienced class. He illustrates how to "read" vectorcardiograms without really burdening the audience with either the boring quantitative data or the confusing grey zones between normal and abnormal. Some new material (timed vectorcardiograms) is added to give the illusion of being at the frontier of the field. A few esoteric examples are given at the end for an aura of comprehensiveness. Thus, the book deserves a place for those who seek an introductory personalized lecture series on vectorcardiography. Whether the book serves as a better introduction to vectorcardiography than preexisting texts is debatable. But the book does not deserve a place on the reference shelf to be turned to for help in sorting out problems of vectorcardiographic interpretation.

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obituaries

Herbert H. Schoenfeld
1893-1973

Dr. Herbert H. Schoenfeld, retired brain surgeon and former chairman of the Department of Surgery at Children's Hospital, died August 23, 1973. He resided at 4911 Sedgwick Street, N.W., Washington, D.C.

Born in Berlin, Germany, he attended St. Albans School in Washington, D.C. and received his M.D. degree from George Washington University. He did postgraduate work at clinics in Vienna, Austria, and London, England.

He interned at Children's Hospital, Garfield Memorial Hospital and Emergency Hospital and was on the staffs of Children's Hospital and Garfield Memorial Hospital and was a consulting surgeon on the staffs of St. Elizabeths Hospital and Montgomery County Hospital.

Dr. Schoenfeld taught at both Georgetown and George Washington University medical schools during the past 40 years. As a teacher, he rose from an instructor in surgery to associate clinical professor in surgery.

Dr. Schoenfeld was a Life member of the Medical Society of the District of Columbia; a fellow of the American College of Surgeons; a member of the D.C. Academy of Surgery; the George Martin Kober Medical Society; the Pan American Medical Association and the International Medical Club and a founding member of the Southeastern Surgical Congress.

He is survived by his wife, Genevieve of the home address; a daughter, Mrs. Robert W. Fleming of Spring Hill, Md.; a stepdaughter, Mrs. Beveridge D. Miller of Pemaquid Harbor, Maine; a stepson, Dr. Gregory T. Henesy of Bethesda, Md., a brother, Rudolph E. Schoenfeld of Washington and a sister, Margaret Schoenfeld of Alexandria.

Frederick O. Coe, M.D.
1889–1973

Dr. Frederick O. Coe, Washington-area Radiologist for many years, died September 1, 1973. He resided at 70 Popular Avenue, Ross, California.

Born in Edison, Ohio, he received his Bachelor of Science degree from Ohio Wesleyan University and his Medical Degree from the College of Physicians and Surgeons, Columbia University. He did postgraduate work in Cytology at the University of Missouri Medical School.

During the First World War, he was a First Lieutenant in the Sanitary Corps, U. S. Army, and Instructor in Radiology, Army Medical School.

He served on the staff of Georgetown University Hospital as Chief of the Department of Radiology, as radiologist at Garfield Memorial Hospital, at Children's Hospital, at Emergency Hospital and at Doctor's Hospital.

A Life member of the Medical Society of D.C., he served on the Society's Board of Censors and its Emergency Medical Service Committee and was a Vice President of the Washington Academy of Sciences. He was a Fellow of the American Board of Radiology, a member of Sigma Xi, the American College of Radiology, the Radiological Society of North America, the American Roentgen Ray Society, and the American Medical Association.

He was also the author of numerous scientific papers in the medical field.

Dr. Coe is survived by his wife Leah, of the home.

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Miller and Smith 2

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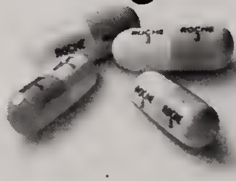

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President's Message
Reflections of an Outgoing President. Irving Burka, M.D. . . 1

Editorial
The Treatment of Breast Cancer. Chandler Smith, M.D. 3

SCIENTIFIC ARTICLES

Cystic Dilatation of the Common Bile Duct in Adults. William L. Joseph, M.D. and Louis Kozloff, M.D 595

Membrane Lung Support in Acute Respiratory Insufficiency. William L. Joseph, M.D., Paul J. Corso, M.D., Glenn W. Geelhoed, M.D., Joseph M. Giordano, M.D., and Paul C. Adkins, M.D 599

Complications of Therapeutic Abortion Utilizing Intra-Amniotic Hypertonic Saline. John Pan, M.D. and David H. Kushner, M.D., F.A.C.S., F.A.C.O.G. 603

Hypohidrotic Ectodermal Dysplasia: An Unusual Presentation. Ronald D. Wilbur, B.A., M.D 605

SPECIAL ARTICLE

Economic Aspects of Drug Over Use
T. Donald Rucker, Ph.D. 609

OTHER FEATURES

Membership Committee Report, Duties and Functions 619

ECG Problems 598

The View Box 602

New Members 621

Book Reviews 623
A Handicapped Child in the Family. (Heisler) Reviewed by W. G. Tompkins, M.D.

Non-Human Primates and Medical Research. (Bourne) Reviewed by Norman C. Kramer, M.D.

(continued)

Alcohol and Health. (HEW Report) Reviewed by Howard M. Silby, M.D.

Progress in Neurology and Psychiatry. (Spiegel) Reviewed by David Satinsky, M.D.

Frontiers in Comparative Medicine. (Spink Lectures) Reviewed by James A. Curtin, M.D.

Current Research in Oncology. (Anfinsen, Potter and Schecter) Reviewed by Bruce I. Shnider, M.D.

Obituaries 627

Charles C. Hageage, M.D.
Leonidas A. Ayton, M.D.

Information for Authors 20

Advertising and Subscription Information 21

Index to Advertisers 22

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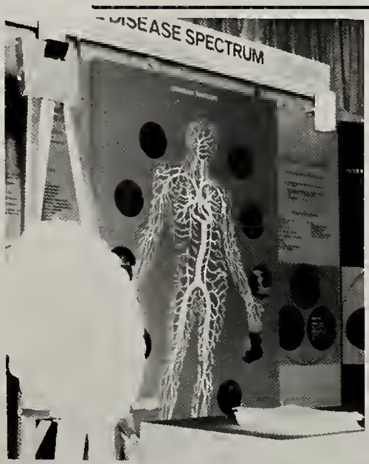

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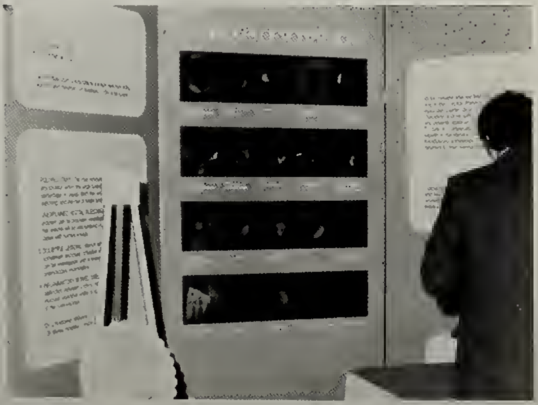

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Reflections of an Outgoing President

IRVING BURKA, M.D.

It is a bittersweet thing that I now do, bidding you au revoir as your President. This has been a most challenging, active and gratifying year for me, as I am sure it was in the past for my predecessors. The Society and its activities appear in an entirely different perspective from the top than from any other vantage point. I regret that all of you were unable to view this panorama with me.

As I reflect upon my experiences during these past twelve months, it dawns upon me that this office will in the near future require the full time attention of the incumbent. Consequently, I would like to suggest for your consideration that we make the office of the President an honorary one. If we are to continue attracting able persons in their prime and in the active practice of medicine to serve, we should consider either compensating the President for income loss or, to reiterate, make the office an honorary one. If the office becomes honorary, then the burden of the everyday activities of the Society would be shifted to the Executive Director who might then be designated as an Executive Vice President.

I hope that we shall continue in the leadership for the improvement of ambulatory care and emergency medical services for this community. I pray that we shall continue to do our utmost to protect and improve the ethics of our profession. It is my hope that we remain innovative in our approach to problem solving–accepting the new when it spells improvement and protecting the old when found to be time tested and proven to be for the betterment of our profession.

And now it is time to thank the many people who helped me so much this year. My sincere thanks to Dr. Darrell Crain and Dr. Marvin Korengold who shared the chairmanship of the Executive Board for this year and all the members of the Executive Board. To the Editors of the ANNALS, Drs. Raymond Scalettar and Robert Smith, and to Dr. John Hughes, the Editor of the Newsletter, for their hard work on their respective publications and their editorial boards.

I wish I could thank the Chairman of every committee and those who served on the committees personally for they are truly the mainstay of our Society, and one could not thank them enough for the time and effort expended on our behalf.

Special thanks must go to our Executive Director Mr. Franc Ferraraccio who was of invaluable help to me during the entire year; to his Assistants, Beth Custer, Doug Torrence, Mike Eason and Roger Mecum. I really don't know how I could have gone through all the intricacies of the office without their continuous help. I would like to thank personally, all of the Secretarial Staff, who are so proficient and efficient: Marjorie Barnard, Pat Mitton, Kathy Heider, Janet Heatwole, Pam Edwards, Therese Fela and Erica Cioffi. My thanks also to Helen Workman, Edna Fry and Shirley Hefner, manager of the Medical Bureau; Mr. Earl Jennings and Yolanda Ballesteros of the accounting department, and Jeannie Tucker in circulation department.

I would like on behalf of the Society to greet our new President, Dr. Clifton Gruver and to wish him and all of you a happy, healthy, and joyous New Year.

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The Treatment of Breast Cancer

There are two ways of selecting the treatment for cancer of the breast. One is reliable, the other is not. The first is according to the rate of survival, the second is according to the principle of treatment. The former is based on the premise that a high rate of survival equates with a favorable accomplishment of the method, and that a comparison of survival rates will reveal the superior method. This analysis has not succeeded, however, and there is presently controversy over the place of "lumpectomy", simple mastectomy, and radical mastectomy in the treatment of breast cancer.

The second way is different. It is based on four premises, i.e., that the cancer arises in the breast, that it later spreads away from that site, that the extent of the spread cannot be determined accurately, and that cure requires the ablation of all of the tumor. From these premises the principle of treatment naturally follows; it is the ablation of the primary tumor and the largest amount of expendable tissue adjacent to it at the earliest possible time. The method cannot be so radical, of course, as to jeopardize the recovery of the patient, and it cannot be so conservative as to allow recurrence because of failure to ablate tumor from expendable tissue.

If all of the tumor lies within the tissue ablated by the method, the patient survives. If some of the tumor has spread beyond the tissue ablated by the method, the patient succumbs. Survival for the individual is thus determined by the spread of the tumor at the time of treatment. If the spread of the tumor determines the survival of the individual, it also determines the survival of the group. The rate of survival therefore indicates the proportion of the group in which all of the tumor was localized within the tissue ablated by the method. The rate of survival thus expresses a cumulative localization of tumor within a group of patients.

This definition affects the interpretation of survival rates. When simple mastectomy achieves a high result, it does not certify a superior method, it indicates a localization of tumor within the tissue ablated by that method in most of those patients. When radical mastectomy achieves a high result, it does not certify a superior method, it indicates a particular localization of the tumor in most of those patients. A low result after either method is not due to a fault of the method so much as to a frequently deep spread of the tumor. Survival rates thus express tumor localization, and they may be high or low regardless of whether the method is conservative or radical. Survival rates are thus an unreliable index of the quality of the method, and a comparison of survival rates is not a comparison of the quality of two methods of treatment, it is a comparison of the distribution of tumor in two series of patients. That is an unsound way of identifying the superior method.

So long as the cancer spreads only away from the site of origin, and cure requires the ablation of all of the tumor, the result of treatment cannot be improved by reducing the amount of tissue ablated by the method, or by delaying the application of it. The superior method is therefore that which most closely complies with the principle of treatment. This is valid regardless of the rate of survival. For example, when a conservative method achieves a high result, it cannot be denied that a radical method used in its place might have achieved an even higher result. On the other hand, after radical treatment, it cannot be claimed that conservative therapy applied to those same patients could have improved that result. There is accordingly no way for a comparison of survival rates to establish the superiority of conservative treatment, or to vitiate the superiority of radical treatment, and massive undertakings for this purpose have no way of succeeding. It may be concluded that whenever the method fulfills the stipulations of the principle of treatment, the result cannot be improved by any method that does less. The superior treatment is accordingly not that which achieves the higher rate of survival, but that which most closely complies with the principle of treatment.

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This definition affects the interpretation of survival rates. When simple mastectomy achieves a high result, it does not certify a superior method, it indicates a localization of tumor within the tissue ablated by that method in most of those patients. When radical mastectomy achieves a high result, it does not certify a superior method, it indicates a particular localization of the tumor in most of those patients. A low result after either method is not due to a fault of the method so much as to a frequently deep spread of the tumor. Survival rates thus express tumor localization, and they may be high or low regardless of whether the method is conservative or radical. Survival rates are thus an unreliable index of the quality of the method, and a comparison of survival rates is not a comparison of the quality of two methods of treatment, it is a comparison of the distribution of tumor in two series of patients. That is an unsound way of identifying the superior method.

So long as the cancer spreads only away from the site of origin, and cure requires the ablation of all of the tumor, the result of treatment cannot be improved by reducing the amount of tissue ablated by the method, or by delaying the application of it. The superior method is therefore that which most closely complies with the principle of treatment. This is valid regardless of the rate of survival. For example, when a conservative method achieves a high result, it cannot be denied that a radical method used in its place might have achieved an even higher result. On the other hand, after radical treatment, it cannot be claimed that conservative therapy applied to those same patients could have improved that result. There is accordingly no way for a comparison of survival rates to establish the superiority of conservative treatment, or to vitiate the superiority of radical treatment, and massive undertakings for this purpose have no way of succeeding. It may be concluded that whenever the method fulfills the stipulations of the principle of treatment, the result cannot be improved by any method that does less. The superior treatment is accordingly not that which achieves the higher rate of survival, but that which most closely complies with the principle of treatment.

The radical method is superior to the conservative method by the number of patients in whom the tumor has spread to the axilla but not beyond. Although this number is likely small, for those patients, the choice of method is critical. It is not possible for the physician to identify the patient with this particular distribution of tumor at the time the method of treatment is selected. Therefore, in order to provide all patients with the highest prospect for cure, it is necessary, under optimal conditions, to select the radical method regularly. If for some cosmetic or other reason the patient wishes to preserve her axilla, that is an option she is free to choose so long as it is understood that her prospect of cure is reduced by a small degree on this account. But it is unacceptable for the physician to recommend a method known not to provide the highest prospect for cure. That is a violation of the trust the patient places in her physician.

It is concluded that the method of treatment for carcinoma of the breast should be selected according to compliance with the principle of treatment rather than by a comparison of the rates of survival. This allows needless exertions to be avoided on the one hand, and it guarantees for all patients the highest prospect for cure on the other.

CHANDLER SMITH, M.D.

1973 Scientific Assembly, Statler Hilton, Oct. 12-13, 1973. At Annual Dinner Dance (left to right), Dr. and Mrs. Irving Burka; Dr. and Mrs. Clifton Gruver; and Mr. and Mrs. F. P. Ferraraccio.

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Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
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The Executive Committee of the National Association of Retail Druggists

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The National Wholesale Druggists' Association

J int Statement on Antisubstitution Laws and Regulations

The purpose of this statement is
affirm the support of the participat-
organizations for the laws, regula-
ns and professional traditions which
ohibit the unauthorized substitution
drug products.

Traditionally, physicians, den-
ts and pharmacists have worked
operatively to serve the best inter-
ts of patients. Productive coopera-
n has been achieved through
utual respect as well as a common
ncern for the ideals of public
rvice. This mutual respect has been
lected, in part, by joint support
er the years for the adoption and
forcement of laws and regulations
ecifically prohibiting unauthorized
bstitution and encouraging joint
scussion and selection of the
urce of supply of drug products.
e basic principles of medical, den-
and pharmacy practice are thus
lized and preserved in the interest
patient welfare.

The antisubstitution laws have
t obstructed enhancement of the
ofessional status of pharmacy any
ore than they have in and of them-
lves guaranteed absolute protec-
n from unsafe drugs, or freed
ysicians, dentists and pharmacists
om their responsibilities to patients.
a practical matter, however, such
vs and regulations encourage inter-
ofessional communications regard-
g drug product selection and assure
ch profession the opportunity to
ercise fully its expertise in drug
age, to the advantage of patients.

Physicians and dentists should
urged to increase the frequency
d regularity of their contacts with
armacists in selection of quality
ug products, recognizing that economies to patients can be improved through such communication, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physicians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selection remain primary and do not permit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved understanding and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthorized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

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ntraindications: Contraindicated in pa- ts previously found hypersensitive to spec- mycin.

rnings: Not indicated for the treatment of hilis. Antibiotics used to treat gonorrhea mask or delay the symptoms of incubating hilis. Patients should be carefully examined monthly serological follow-up for at least onths should be instituted if the diagnosis of syphilis is suspected.
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Dosage and administration: Keep at 25° C and use within 24 hours after reconstitution with diluent.
Male—Inject 5 ml intramuscularly for a 2 gram dose. Patients with gonorrheal proctitis and patients being re-treated after failure of previous antibiotic therapy should receive 4 grams (10 ml). In geographic areas where antibiotic resistance is known to be prevalent, initial treatment with 4 grams (10 ml) intramuscularly is preferred.
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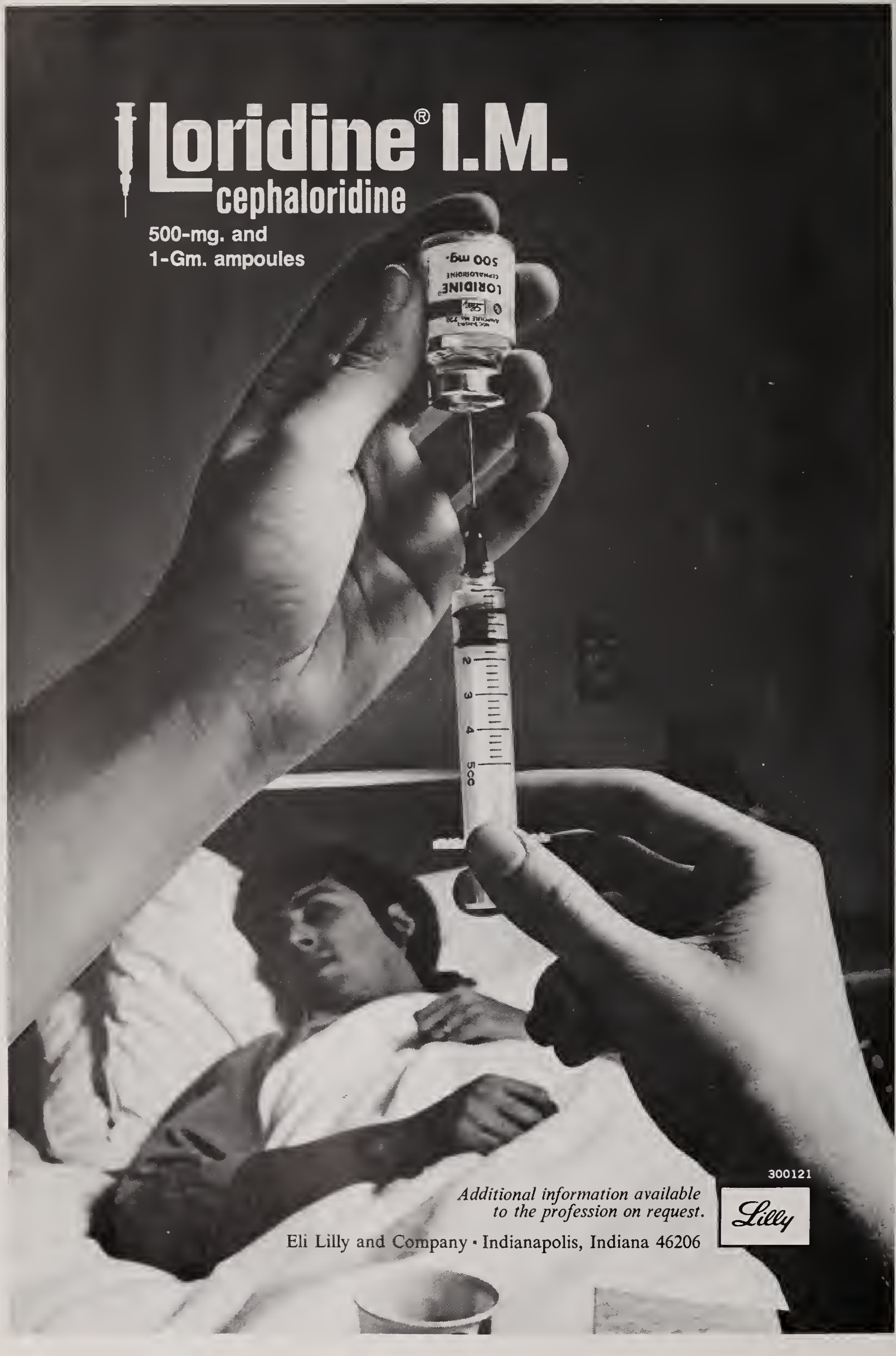
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Cystic Dilatation of the Common Bile Duct in Adults

LOUIS KOZLOFF, M.D.* AND WILLIAM L. JOSEPH, M.D.†

Introduction

Cystic dilatation of the biliary ductal system is an anatomic and clinical entity that has captured the interest of surgeons and anatomists since Vater's original description in 1723[1]. Although relatively uncommon, approximately 500 cases of choledochal cyst have been reported in the literature[2]. The majority of these reports have stressed that this lesion is congenital in origin, initially found in children and young adults, and characterized by the classic triad of abdominal pain, jaundice, and an abdominal mass. More recent experience has suggested, however, that this lesion may be acquired in origin, occurring in an older group of patients who frequently have a long history of biliary tract symptoms[3,4]. The present report outlines the authors' experience with five new cases of cystic dilatation of the common bile duct in adults.

Case Material

Case # 1: A 27 year-old female was seen with a 3½ year history of recurrent right upper quadrant pain associated with intermittent jaundice, dark urine and light-colored stools. She was subsequently admitted to the hospital where an exploratory laparotomy was performed with a preoperative diagnosis of chronic cholecystitis. At the time of laparotomy, a large stone was palpated in the gall bladder. An operative cholangiogram revealed multiple biliary cysts of the right and left main intrahepatic bile ducts and a fusiform dilatation of the common bile duct above the duodenum without evidence of distal obstruction. Cholecystectomy and Roux-en-Y choledochocystojejunostomy were performed. Her postoperative course proceeded uneventfully and the patient has had no additional biliary symptoms over the last eight years.

Case # 2: A 39 year-old woman was admitted with a two year history of intermittent right upper quadrant pain associated with nausea, vomiting, fever, episodic jaundice, and longstanding fatty food intolerance. At laparotomy, cholecystectomy was performed and a single large stone found within the gallbladder. Operative cholangiography was done and showed cystic dilatation of the common bile duct just above the duodenum. Choledochocystoduodeneostomy was performed. The patient did well for approximately six months, at which time she experienced recurrent bouts of cholangitis and jaundice. At the time of reoperation, the biliary-duodenal anastamosis was found to be patent, but a large amount of sludge and stones had reaccumulated within the cyst. Liver biopsy revealed cholangitis. The previous anastamosis was taken down, and a Roux-en-Y choledochocystojejunostomy performed. Her post-operative course was free of complications and 2½ years postoperatively she has remained free of recurrent symptoms.

Case # 3: A 41 year-old white woman was evaluated with a ten year history of intermittent right upper quadrant pain associated with nausea, vomiting, jaundice, light-colored stools and dark urine. Four years prior to this admission she had undergone cholecystectomy with common bile duct exploration at which time a normal gallbladder was found. Results of the common bile duct exploration were unknown to the patient. On the present admission, she complained of increasing severity of her symptoms. Laboratory data revealed a total bilirubin of 4.1 mg per cent (direct 2.1), alkaline phosphatase of 31 KA units, and a normal amylase. At operation a fusiform choledochal cyst of the common bile duct was noted and confirmed on operative cholangiography. Liver biopsy showed mild biliary cirrhosis. Roux-en-Y choledochocystojejunostomy was performed, with satisfactory results.

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Case # 4: A 51 year-old woman was admitted in 1970 for recurrent attacks of right upper quadrant pain and a history of fatty food intolerance. In 1965 she had undergone cholecystectomy and a diagnosis of chronic cholangitis made. In 1967 and 1968 common bile duct explorations were performed, both of which were negative. She continued to have recurrent bouts of cholangitis and in 1970 was re-explored. Operative cholangiography revealed a localized diverticulum of the distal duct in which were found numerous small stones, sludge, and coagulated bile. The cyst was excised and the patient's recovery progressed uneventfully. She has had no recurrence of her symptoms to date.

Case # 5: A 24 year-old white woman was admitted with a two to three year history of recurrent right upper quadrant and midepigastric pain, weight loss, diarrhea, and fever. Eighteen months prior she had undergone cholecystectomy, at which time a chronically scarred gallbladder was noted, without stones, but containing soft particulate matter. An operative cholangiogram revealed the presence of a choledochal cyst and a choledochocystoduodenostomy was constructed at that time. On the present admission, all laboratory studies were within normal limits. Upper GI series showed retrograde filling of the cyst and the hepatic duct radicals through a patent biliary-duodenal anastamosis (Fig. 1). At operation, a six centimeter cyst was identified and found to contain a large amount of undigested food, barium, and coagulated bile. Soft bilirubin stones were present. The previous anastamosis was taken down and a Roux-en-Y choledochocystojejunostomy performed. Her postoperative course was uneventful and she continues to be asymptomatic.

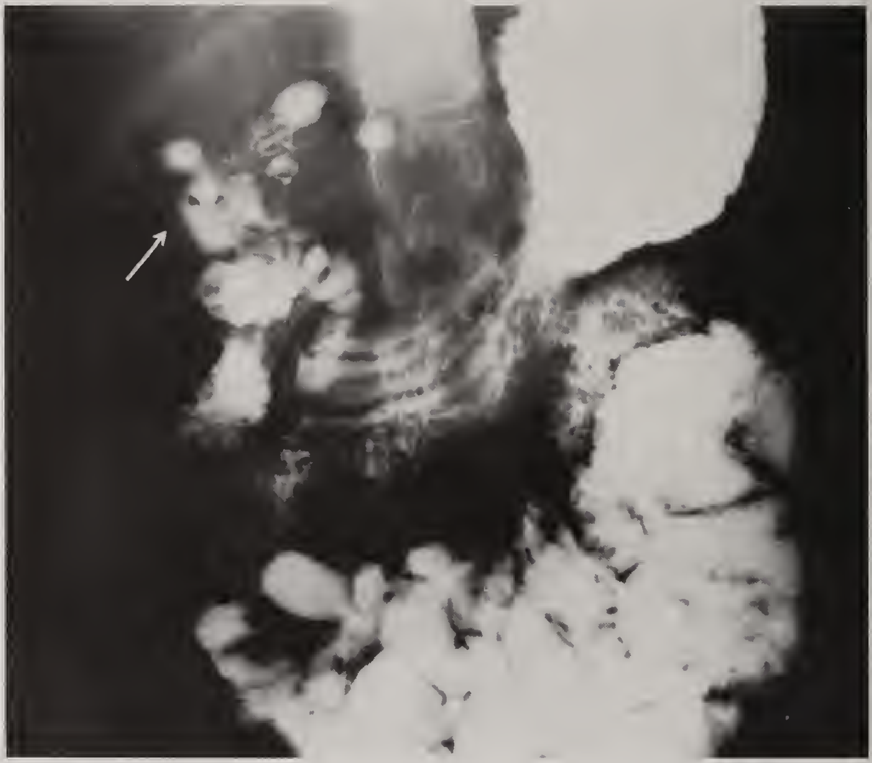

Fig. 1. Upper gastrointestinal series in patient with choledochocystoduodenostomy showing reflux of barium into the choledochal cyst and hepatic radicles.

Discussion

Idiopathic cystic dilatation of the common bile duct is a well-recognized clinical entity. Many theories have been advenced to explain the etiology of choledochal cysts[2]. Basically, the congenital theory presupposes a congenital weakness or hypoplasia of a segment of the developing bile duct. The actual cyst forms secondarily when a distal obstructive factor appears. Another etiologic theory postulates an excessive epithelialization of the bile duct outgrowth; then, when canalization of the lumen occurs, a cystic space is left. In addition, it is probable that some instances of cystic biliary dilatation are entirely acquired in origin and are secondary to partial distal biliary obstruction caused by gallstones, strictures or tumors.

The majority of cases have occurred in the pediatric age group and thus have been considered developmental in origin. Whether the formation of the cyst is congenital or acquired, it is obvious that many patients may remain free of clinical disease until adulthood. In 1965 Joseph, Fonkalsrud, and Longmire[3] stressed the occurrence of choledochal cyst in adults, reporting on two such cases. More recently, Trout and Longmire[4] reviewed the literature and presented 61 cases with five-year follow-up data, fourteen of which occurred in adults. Glenn and McSherry[5] reviewing fifteen cases at the New York Hospital-Cornell Medical Center over a 31 year span, found seven of these cases in adults.

Zinninger and Cash[6] stressed the symptomatic triad of right upper quadrant pain, jaundice and a palpable mass. The presence of an abdominal mass has proven to be the most inconsistent component of this triad, occurring in none of the five patients in the present group of patients (Table 1). Other series have confirmed this finding, reporting anywhere from a 58 to 77% occurrence of a palpable tumor[3,7,8]. Adult patients more commonly present with symptoms indistinguishable from those reported by patients with calulous biliary tract disease—namely intermittent jaundice and cholangitis. In addition, many of these individuals have a prior history of previous biliary tract operations.

TABLE 1: Clinical Summary of Patients with Choledochal Cyst

Case #	Age (yrs.)	Duration of symptoms (yrs.)	Pain	Jaundice	Mass	Operation
1.	27	3½	+	+	0	Roux-Y
2.	39	2	+	+	0	Roux-Y*
3.	41	10	+	+	0	Roux-Y
4.	51	5	+	+	0	Excision
5.	24	3	+	+	0	Roux-Y*

* denotes patients with previous choledochocystoduodenostomy.

The diagnosis of choledochal cyst can be difficult, and may even be missed intraoperatively. In our own cases the diagnosis was ultimately confirmed with a combination of exploratory laparotomy and operative cholangiography. Radiographic demonstration of the cyst becomes important in several instances: (a) where scarring and distortion from previous surgery and inflammation makes identification of the biliary radicals difficult, (b) in diverticular-type choledochal cysts of the biliary tree which can be anatomically obscure, (c) in cases where the cystic dilatations are within the duodenal wall or are intrahepatic, and (d) in an effort to identify associated biliary tract anomalies.

Although most agree that the primary treatment of choledochal cyst is surgical, there is some disagreement about the procedure of choice. A diverticular-like cyst with a narrow neck (as in Case #4) may be excised in most instances. Cysts within the duodenal wall are best drained into the duodenum. Cystic dilatation of the common duct and those involving the cystic and hepatic ducts can be managed by excision or an internal drainage procedure. Cyst excision has been favored primarily by the Japanese with acceptable results[8]. Critics of this operation point to a higher mortality because of the high incidence of associated anomalous bile ducts and blood supply as well as pancreatic ductal injury. Drainage of the cyst into the gastrointestinal tract is the most frequent method of treatment. Gross[9] and Maingot[10] consider choledochocystoduodenostomy as the most acceptable procedure. While the initial mortality with this method is low, there is a 12 to 30% incidence of recurrent cholangitis from reflux into the cyst from the duodenum (as in Cases # 2 and 5). Roux-en-Y choledochocystojejunostomy is the alternate method of cyst decompression. The cysto-jejunostomy stoma is established in the distal dependent portion of the cystic dilatation and proximal to the choledochoduodenal junction. It also has a low mortality but with a reduced risk of reflux cholangitis[11,12]. Our experience with cyst decompression in the Roux-en-Y fashion leads us to favor this method of therapy. In addition, the present authors suggest that in those individuals who develop cholangitis following choledochocystoduodenostomy, consideration be given to revision of the cystoenterostomy and construction of a Roux-en-Y jejunal limb.

Summary

Five adult patients with idiopathic cystic dilatation of the common bile duct are presented, all of whom eventually underwent exploratory laparotomy. Several conclusions can be drawn from the present series:

(1) Cystic dilatation of the biliary ductal system, formerly considered a pediatric disease, can present initially in adulthood.

(2) The classic triad of right upper quadrant pain, jaundice, and a palpable abdominal mass is not uniformly present. More commonly, older patients present with symptoms of chronic relapsing cholangitis and jaundice, without a palpable mass.

(3) Operative cholangiography is a valuable adjunct to diagnosis, and may confirm the presence of a choledochal cyst even when not evident intraoperatively.

(4) Roux-en-Y cystojejunostomy appears to be the procedure of choice when simple cyst excision is not practical.

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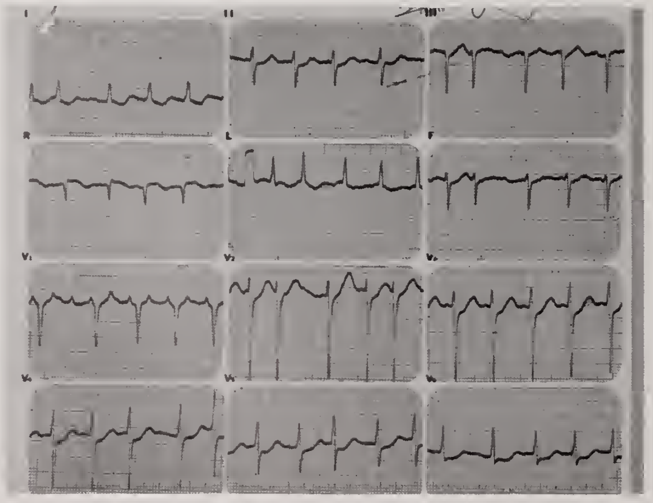
ECG Problems

HISTORY: Sixty-eight-year old, white female with a history of rheumatic heart disease since age 16 was admitted with rapid heart action. She had been taking Digoxin 0.25 mg. five days per week since an episode of congestive heart failure two years previously. The patient was not aware of this rapid heart action. It was discovered at an examination preceding a trip abroad.

(for diagnosis see page 614)



Membrane Lung Support in Acute Respiratory Insufficiency

**WILLIAM L. JOSEPH, M.D.,* PAUL J. CORSO, M.D.,† GLENN W. GEELHOED, M.D.,‡
JOSEPH M. GIORDANO, M.D.§ AND PAUL C. ADKINS, M.D.****

Pulmonary problems play a major role in the morbidity and mortality of all seriously ill patients. Recent advances in intensive care management and mechanical ventilatory support have significantly reduced the mortality in many of these patients who develop acute respiratory failure. Nevertheless, a number of these individuals become refractory to the standard modes of respiratory assistance and continued high inspired oxygen concentrations may produce additional pulmonary parenchymal damage. The recent development of disposable membrane lung oxygenators appears to be a valuable tool for long-term artificial extracorporeal oxygenation in potentially reversible pulmonary insufficiency among patients unresponsive to standard medical therapy. The present report outlines the authors' experiences with the use of extracorporeal membrane lung bypass as a treatment for the failing lung.

Case Material and Technique

Eight patients with severe respiratory insufficiency were evaluated for continuous membrane lung support; one had a cardiac arrest in the operating room and expired prior to insertion of the bypass cannula while the remaining seven underwent extracorporeal oxygenation which varied from six hours to five days (Table 1). Indications for initiating this form of therapy in hypoxemic patients were: 1) failure of conventional therapy, 2) PO_2 less than 40 mmHg despite an FIO_2 of 100% on a volume-controlled ventilator, 3) hypoxemic cardiovascular or central nervous system deterioration, 4) no evidence of uncontrolled bleeding, 5) potentially reversible pulmonary failure.

A venovenous bypass technique using the General Electric (G.E.)–Peirce membrane lung was employed in four patients. Under local anesthesia a wire reinforced vinyl cannula was inserted at the sapheno-femoral vein junction and positioned well up into the inferior vena cava. Through a separate neck incision, a second cannula was placed in the superior vena cava via the internal jugular vein. Each patient received 1.5 mg/Kg of heparin prior to cannulation; careful attention was paid to sterile technique and meticulous hemostasis. The extracorporeal circuit was primed with fresh pre-typed whole blood. Blood priming volume and oxygen supply flow rates varied with the size of the membrane lung employed. Blood was circulated via the inferior caval catheter through a venous reservoir and pumped into the membrane lung. After oxygenation, an arterial pump passed the blood through a bubble trap and back to the right atrium. In the remaining three individuals, venoarterial bypass was utilized. In this instance an additional cannula was inserted at the groin into the femoral artery and advanced upward into the abdominal aorta. Blood flow was circulated via both caval catheters through the extracorporeal circuit and the oxygenated blood returned to the aorta. Body temperatures was controlled between 35-37 degrees C, by a heat exchanger in the oxygenator. As soon as possible after initiation of bypass, patients were ventilated with 40-50% inspired oxygen. Manometers recorded inlet and outlet pressures in

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TABLE 1: Membrane Lung Support–G.W. Series

Patient	Age	Pulmonary Lesion	Bypass	Perfusion Time	Bypass Flow	Systemic PO_2 Prior to Bypass	Systemic PO_2 on Bypass	Results
H.W.	38	Bacterial pneumonia	V-V	6 hours	1.5 L/min	31 mmHg	49 mmHg	Poor flows–bypass stopped
V.B.	66	Bacterial pneumonia	V-V	8 hours	2 L/min	38 mmHg	42 mmHg	Poor flows–bypass stopped
G.W.	11	P. carinii pneumonia	V-V	4½ days	900 cc/min	37 mmHg	57 mmHg	G.I. bleeding
C.R.	36	P. carinii pneumonia	V-V	5 days	2.3 L/min	31 mmHg	54 mmHg	Long-term survivor
S.W.	35	P. carinii pneumonia	V-A	18 hours	2.5 L/min	48 mmHg	75 mmHg	Cardiac arrhythmia and arrest
N.B.	49	"Shock lung"	V-A	15 hours	3.0 L/min	46 mmHg	68 mmHg	Irreversible lesion and renal failure
C.R.	32	"Shock lung"	V-A	75 hours	5-8 L/min	44 mmHg	89 mmHg	Hemorrhage from trachea–innominate artery fistula

V-V: venovenous bypass
V-A: venoarterial bypass

the circuit. In addition, a second standby lung was mounted in parallel in case of leakage or use should the patients oxygen demand require it. A flow meter on the heart-lung machine monitored bypass flow rates. All patients were kept in the Special Care Unit where catheters were inserted for continuous monitoring of central venous, pulmonary artery, wedge, and arterial pressures. Arterial blood gases, clotting studies, and cardiac outputs were performed at intervals varying with the patient's condition. All data were recorded on an Alpha 21 analog and digital computer. Maintenance heparin dosage was 0.5 mg/Kg/hr. which maintained a Lee-clotting time of 25-30 minutes.

Results

In all cases, the extracorporeal membrane lung circuit performed well with effective oxygenation of the venous blood thereby allowing a reduction in the high inspired oxygen concentrations from the ventilator prior to the bypass. Clotting in the unit was not seen. Although adequate bypass flows were initially obtained in the first two patients with an increase in systemic arterial PO_2, venous inflow soon fell to less than 500 cc/min–a rate inadequate to sustain both patients, and bypass was discontinued. In retrospect, both of these individuals had severe central nervous system and cardiac deterioration suggesting that bypass should have been instituted earlier. The remaining two patients undergoing venovenous bypass had a more satisfactory response. Both had an increase in systemic arterial PO_2 (greater than 50 mmHg) sufficient to maintain adequate tissue oxygenation with a reduction in FIO_2 to safe concentrations. At four and one-half days, patient G. W. developed gastrointestinal bleeding which required discontinuing bypass, and he subsequently expired. Patient C. R. was able to maintain an arterial PO_2 of 57-60 mmHg on 50% oxygen after five days of extracorporeal membrane support and was discharged from the hospital two weeks later.

The remaining three patients were supported by venoarterial bypass for periods of 15-75 hours diverting 50-80% of their cardiac outputs through the extracorporeal circuit (G.E.-DUALUNG). Prior to support, each of these patients had a progressive fall in arterial PO_2, despite an FIO_2 of 100% and 10-15 cm. of PEEP. In fact, two of these individuals (S. W. and C. R.) had developed a pneumothorax, subcutaneous emphysema and persistent air leakage as a result of an increase in PEEP. All had a marked elevation in arterial PO_2 (68-89 mmHg) while on bypass. Patient S. W. sustained a cardiac arrest and could not be resuscitated while patient N. B. had a progressive decline in his own lung function requiring additional support from the membrane lung unit. A needle biopsy of the lung revealed hyaline membranes consistent with "respirator lung" and bypass was discontinued. The last patient (C. R.) had 5-8 liters/min diverted through the extracorporeal circuit. Her arterial PO_2 rose from 44 to 89 mmHg (at the aortic arch) and she awakened from her semi-comatose condition and responded to questions. However, at 75 hours, she developed profound hypotension as a result of a trachealinnominate artery fistula and expired.

Discussion

Although basic blood oxygenators have been utilized for many years, for open-heart surgery, these devices have a direct blood gas interface which produces serious blood damage during periods of extended perfusion. The recent development of a blood-gas exchange based on a membrane separation allows prolonged extracorporeal oxygenation with much less blood damage.[1] Present day membranes generally constructed of silicone copolymers appear to be of adequate structural strength with reliable gas exchange and a relative lack of toxic effects to the blood elements. Currently a number of portable disposable membrane oxygenators are available.[2,3,4]

At the present time, a number of clinical studies are in progress utilizing membrane lung support in the treatment of acute respiratory failure. At least 30 patients have had prolonged temporary lung support.[5] The longest survivor is a patient with acute leukemia who developed severe pneumonia and subsequent hypoxia (PO_2 35 despite FIO_2 of 100% with 15 cm of PEEP). After nine and one-half days of venovenous bypass (by Kolobow[6]), he was able to maintain satisfactory systemic oxygenation on 40% O_2. Other perfusions have been documented by Peirce[7], White[8] and others.[5] Probably the most extensive experience has been reported by Hill.[9] He has perfused fifteen patients who developed acute respiratory failure secondary either to "shock lung," fat embolism, respiratory burn or pneumonia. Adequate oxygenation was obtained in all cases; five patients were satisfactorily taken off bypass while three are long-term survivors. As in the present series, the major difficulty is to institute extracorporeal membrane lung support as early as possible. As yet, criteria are still vague as to when an individual becomes unresponsive to conventional medical therapy. The present series and the extensive experience of Hill[9] and Kolobow[3] point out the beneficial effect of membrane lung support if instituted early. Prolonged heparinization is still a potential complication of bypass. Lower heparin dosage schedules and the technique for the rapid determination of activated clotting time (method of Hattersley) will hopefully reduce this risk.[9]

There is still some speculation as to the best configuration for membrane lung support. Venovenous perfusion—as employed in the first four patients—has the least chance of hemodynamic disturbance and allows an even distribution of oxygen. Its major disadvantage is that it provides no hemodynamic benefit to the failing heart and lung. As can be seen by our own cases, the increase in arterial PO_2 never exceeded 15-20 mmHg. In addition, unsatisfactory support of the first two cases was due to congestive heart failure and an inability to relieve the right side of the heart. On the other hand, venoarterial membrane support provides maximal hemodynamic benefit to the cardiopulmonary system and thereby allows the lung to be placed in a better environment for recovery. In our last three patients, 40-80% of the cardiac output could be diverted through the extracorporeal circuit with immediate improvement in systemic oxygenation (mean – 75 mmHg). In addition, a fall in pulmonary artery pressure and increase in effective compliance was seen with venoarterial bypass. Our own experience as well as Hill's,[9] suggest that in most instances, venoarterial membrane lung support provides the most benefit to the patient.

Summary

Current developments in membrane lung designs have now allowed long-term extracorporeal pulmonary support to be performed with a minimum of complications. Seven cases are presented which demonstrate the clinical usefulness and indications for external oxygenation. At present, this represents the second largest clinical experience in the world. With increased experience, temporary use of an artificial extracorporeal lung will be a practical approach in the patient with potentially reversible pulmonary failure unresponsive to conventional therapy.

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THE VIEW BOX

Prepared by
The Department of Radiology
Washington Hospital Center

A middle-aged male complains of right-sided flank pain and repeated urinary tract infection. As part of the work-up, Excretory Urograms and a right-sided Retrograde Pyeloureterogram were done.

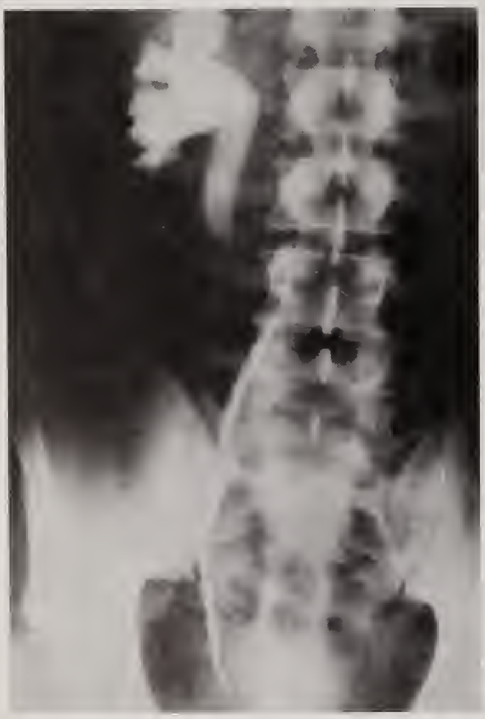

Fig. 1. Right-sided retrograde pyeloureterogram.

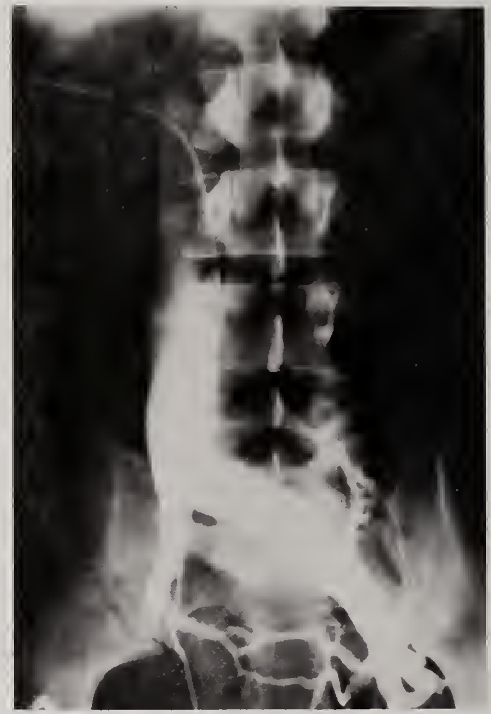

Fig. 2. Venogram of the Inferior vena Cava with a catheter in the right ureter.

(for diagnosis see page 628)

Complications of Therapeutic Abortion Utilizing Intra-Amniotic Hypertonic Saline

JOHN PAN, M.D.* AND DAVID H. KUSHNER, M.D., F.A.C.S., F.A.C.O.G.*

Transabdominal intra-amniotic instillation of hypertonic saline solution 23% has become an accepted treatment for the termination of pregnancy. The instillation of urea (Raud)[1] and prostaglandin has also been successful. Fifty percent hypertonic glucose solution instillation is no longer used due to the frequency of sepsis caused by *Clostridium welchii* (Shulman).[2] Most saline abortions are performed as an in-hospital procedure, but they have been done as an out-patient procedure (Schulman).[2]

The action of intra-amniotic injections following withdrawal of amniotic fluid is not yet understood. Csapo's concept is that hypertonic saline infusion terminates pregnancy because it suppresses placental progestogenesis, disturbs the transportation of the hormones in the fetal membranes, increases uterine volume, and in so doing weakens the progesterone block and promotes the evolution of uterine activity and oxytoxin response (Hoch).[3] Weiss et al[4] report changes in coagulation factors with decrease in platelets, fibrinogen and fractions VIII and V. As there is a spectrum of diffuse intravascular coagulation, the resulting defibrination process may cause a clinical bleeding diathesis.

Table I

Complications	JPSA	Columbia hospital
Retention of placenta	2,356 (16.0%)	110 (13.4%)
Transfusion	171 (1.2%)	8 (1%)
Fever	1,189 (8.1%)	33 (4.0%)
Mortality	2	0

Technique

Local infiltration of skin and fascia with 1% Xylocaine is used. A 3-1/2 or 6-1/2 inch #18 gauge needle is inserted into the amniotic sac. Fifty to 200cc of amniotic fluid is withdrawn. If blood is obtained on initial aspiration, an alternate site is selected. If failure occurs after four insertions, the patient should have a sonogram to precisely determine the period of gestation and position of the placenta. Depending on the stage of gestation, the patient should be rescheduled within one to three weeks. After several weeks, the amniotic fluid may be discolored, but this should not deter the continuation of the procedure. We do not use the catheter technique, but flushing with the saline solution is occasionally performed. A test injection of 10cc of 23% saline is made slowly. The vital signs are observed. If the patient complains of pain or any untoward symptom, the injection should be discontinued immediately. Otherwise, 150-200cc of 23% saline is injected into the amniotic cavity. A venous angiocath is inserted and a solution of four units of oxytoxin (Pitocin) and 1000cc of 5% dextrose and water is infused. A flow rate of 200cc an hour is continued until the fetus and placenta are expelled and for one hour thereafter to control bleeding. Careful gross examination is made of the products of conception. No curettage is necessary and the patient is discharged.

Results

The Joint Program for the Study of Abortion (JPSA) (Teitze and Lewit), in which Columbia Hospital, Washington, D.C., participated, reported 72,988 induced abortions with 14,690

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saline amniocenteses (20%). Columbia Hospital performed 6,271 abortions from January 1, 1969 to June 30, 1972, with no mortality. There were 818 saline instillations (13%). JPSA reports about one-third of the saline injections as failures, most at comparatively early stages of gestation. This is easily understood, inasmuch as about 4,000 procedures were performed between the 13th and 16th week of gestation. Kushner and Marlow[5] discuss the inadvisability of amniocentesis between the 13th and 16th week of gestation.

Table II: Time Interval Between Saline Injection and Abortion in 110 Cases of Retained Placenta:

24 Hours	24-48 Hours	48-72 Hours	72 Hours
44	56	6	4

Ten cases were successfully terminated with injection of 150 and 200cc of saline with the removal of less than 50cc of amniotic fluid. There were three cases complicated by a delayed intra-amniotic bleeding after 20 to 25cc of saline solution had been injected. These patients aborted at home, while awaiting re-admission for repeat amniocentesis.

Complications

There were 110 retained placentas (13.4%) compared to JPSA, which had 2,356 cases of retained placentas (16%). In the JPSA series 1.2% of the cases required transfusion; at Columbia Hospital 1% in the JPSA series had fever (8.1%); at Columbia Hospital, 4%.

The time interval between saline injection and abortion in the 110 cases of retained placenta was less than 24 hours in 44 patients; in 56, 24 to 48 hours; in six, 48 to 72 hours; and in four, more than 72 hours. The amount of saline injected in 110 cases of retained placenta was 50cc to 200cc in 65 cases; 200cc to 300cc in 43 cases; and more than 300cc in two cases.

Discussion

The most common complication of saline aminocentesis is retention of the placenta. Several hours may be allowed to elapse for spontaneous expulsion of placentas but extraction should be performed immediately if there is excessive bleeding. This requires a surgical procedure under general anesthesia with exploration of the uterus. We were unable to determine any variation of technique that modified this complication. All infections were successfully treated with antibiotics and removal of retained secundines. Blood replacement was rarely indicated. Hypofibrinogenemia is a rare complication which rapidly improves after expulsion of the dead fetus.

Routine post-abortion curettage is unnecessary. It may be a dangerous procedure due to possible perforation of the uterus. Only six patients required re-admission for removal of retained secundines following discharge with the diagnosis of completed abortion.

Table III: Amount of Saline Injection in 110 Cases of Retained Placenta:

50-200 cc	200-300 cc	>300 cc
65	43	2

Summary

Intra-amniotic saline infusion is a safe method for induction of abortion. The procedure is best performed in the 16th and 20th week. The removal of 50cc of amniotic fluid and intrauterine instillation of 150–200cc of hypertonic saline, followed by Pitocin intravenous infusion, is the best method. Sonography is used to determine the period of gestation, when indicated. It is valuable in the diagnosis of multiple pregnancy, abnormal uteri, pelvic tumors and position of the placenta.

Retention of the placenta is the most common complication, and the placenta should be extracted before marked blood loss. This is best performed under general anesthesia to permit complete intrauterine exploration. Hysterotomy should be considered only as a method of last resort.

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Hypohidrotic Ectodermal Dysplasia; An Unusual Presentation

RONALD D. WILBUR, B.A., M.D.*

Introduction

Hypohidrotic ectodermal dysplasia (HED) is one of two forms of ectodermal dysplasia. Maldevelopment of teeth and hair is common to both forms; however, the triad of sparse hair, hypodontia or anodontia and inability to sweat characterizes the hypohidrotic variety.

The first description of the anhidrotic form was found in Charles Darwin's book, *The Variations in Plants and Animals Under Domestication.*[1] Darwin related ten cases in a Hindu family which were recorded in 1838 by Widderburn.[2] There were several cases reported of HED between 1848 and 1929. Thurnam[3] first reported two cases and Weech[4] subsequently coined the term "hereditary ectodermal dysplasia". In 1939, Clouston[5] differentiated the hidrotic and the anhidrotic varieties.

The present report is of a seven year old boy diagnosed after a referral for evaluation for mental retardation.

Case Report

J. S., a seven year old black male, was referred to Developmental Services for Mental Retardation because of poor school achievement, speech impediment and mental retardation. Prenatal, natal and postnatal history was noncontributory. Early development was normal except for a delay up to eighteen months in walking and delayed eruption of the two upper central incisors at ten months of age. His teeth have failed to develop further.

Early childhood was notable for several episodes of high fever up to 106° unassociated with infections. Treatment consisted of aspirin and sponge baths. J. S. has never been known to perspire. Mrs. S. stated that he very quickly learned not to venture outdoors during the hot, humid summer days until after sunset. Two siblings, a brother and a sister, are normal. Mrs. S. sweats very little, has a cleft between her upper central incisors and has a sparse amount of hair. Mrs. S.'s mother displayed identical characteristics. There was no history of consanguinity.

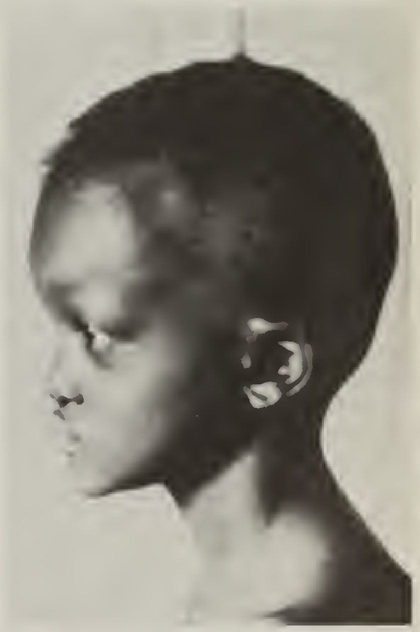

FIG. 1. Note frontal bossing, sparse hair, nasal bridge deformity and prominent lips.

Physical examination revealed a wizened facies, flattening of the occiput and prominence of the forehead (Figure 1). Scalp hair was sparse and silken in quality. The skin was shiny with smooth, thin texture. Eczema was present and there was bilateral wrinkling of the eyelids. Lashes and brows were sparse and scanty. The external ears were deformed. Two peg-shaped, widely spaced upper central incisors were present (Figure 2). The lips were everted and thick and the nasal bridge was low with a saddle-like deformity. The nails were normal. The speech was throaty and hoarse. The right nipple was hypoplastic. Mild expiratory wheezes were audible bilaterally. Phimosis was present.

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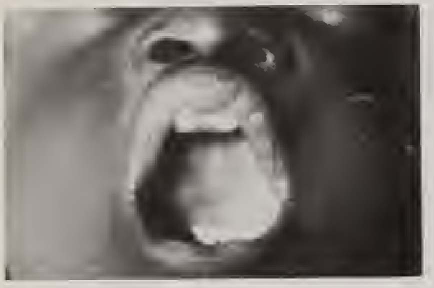

FIG. 2. Upper central incisors. No other teeth present.

Laboratory Studies

Laboratory tests consisting of CBC, Urinalysis, PBI, calcium and phosphorous were normal. X-rays showed a total of two teeth with hypoplastic development of the maxilla and mandible (Figure 3). AP view of the skull showed almost complete lack of turbinate development (Figure 4). Two attempts to elicit sweating by iontophoresis were unsuccessful. Skin biopsy of the lower surface right forearm revealed a total absence of sweat ducts and pylosebacious glands (Figure 5). Dermatoglyphics showed a bilaterally distally placed axial triradius, an extended left proximal transverse crease and bilateral irregular transverse creases of the fingers. A count of the sweat pores was done on J. S., Mrs. S. and an unaffected male sibling. The results (Table 1) show a normal count for the sibling, a partially reduced figure for Mrs. S. and a striking decrease for the propositus.

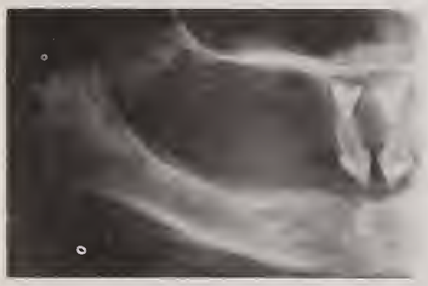

FIG. 3. Panorex view of maxilla and mandible. Primary and secondary upper incisors only teeth noted.

Psychological testing showed J. S. to be normal in intelligence and social competence with average achievements in three major academic areas, i.e. oral reading, spelling, and arithmetic. Distinct signs of emotional imbalance were present and it was felt that he would prove to be a slow learner. It was the psychologist's impression that J. S. displayed adjustment reaction of childhood; conduct disturbance. He was described as an emotionally disturbed child functioning as a slow learner.

Analysis at the Savannah Speech and Hearing Center showed J. to have a severe disorder of articulation characterized by substitutions of initial and medial position consonants and omissions of the majority of final-position sounds. The *h* sound was frequently substituted and was accompanied by nasal air emission. His conversational speech was fairly difficult to understand. He seemed self-conscious about his speech and was reluctant to attempt difficult sounds.

Informal evaluation of his general language performance suggested that he is able to receive, interpret and respond to the speech of others without undue difficulty, with the exception of the poor articulation.

With the exception of dentition, no significant structural difficulties were noted which should interfere with speech production. Pure-tone audiometry revealed normal hearing sensitivity bilaterally.

Discussion

This case of anhidrotic ectodermal dysplasia (HED) was unusual in its mode of presentation. Most patients have been diagnosed either because of the recognition of the cardinal triad and/or minor signs[6] or because of fever of unknown origin secondary to the lack of sweat glands.[7] The occurrence of both mental retardation[8] and normal intelligence[9] in patients with HED has been reported. Although the reason for referral was evaluation of mental retardation, it soon became obvious that, to a great extent, J. S.'s behavior was due to ridicule by his teachers and peers coupled with sharp self-awareness of his speech impediment. As a result, he remained aloof, communicated mainly with negative and positive monosyllables and hesitated to speak in sentences. Also, it soon became apparent that recognition and acceptance of his physical appearance and speech impediment without ridicule resulted in verbal communication in full and reasonably grammatical sentences. The diagnosis was suspected early because of the presence of the cardinal signs of hypotrichosis, hypodontia and anhidrosis coupled with other signs including lip eversion, delicate, smooth, thin skin, eczema, wrinkled eyelids, frontal bossing, saddle-shaped nose and hypoplastic nipple. Diagnosis was firmly established by the lack of sweating on iontophoresis, compatible dental x-rays and

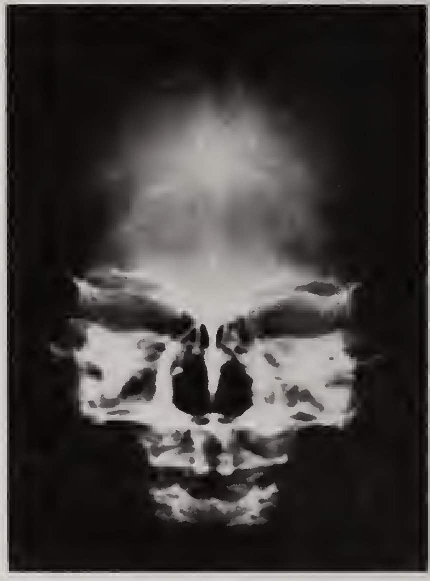

FIG. 4. AP view of skull. Note radiologic absence of turbinates.

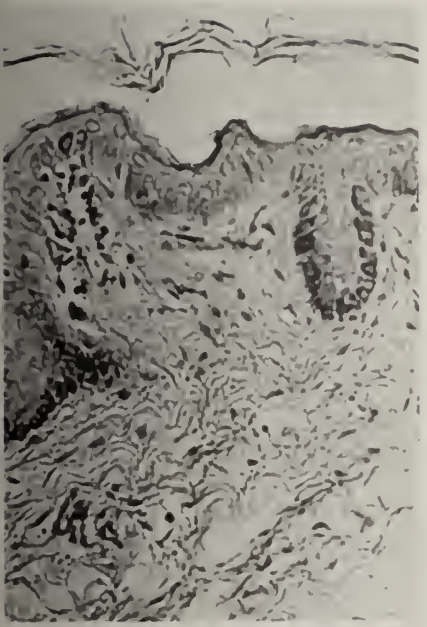

FIG. 5. Skin biopsy demonstrating lack of sweat ducts.

confirmatory skin biopsy. Failure of development of the turbinates was an interesting finding which was not previously reported. HED must be differentiated from several diseases which may have similar characteristics. Congenital syphilis was once thought to be the etiology of HED. Our patient had a negative STS. Hypothyroidism may simulate the skin, hair and voice characteristics. Elevated PBI has been previously reported[10] but found to be normal in other cases.[11] This patient had a normal PBI. The skin and hair may be altered in a similar fashion by idiopathic hypoparathyroidism, but HED has normal calcium levels, as did our patient. Patients with progeria exhibit a similar facial appearance, similar skin and sparse hair growth, but this was eliminated by the involvement of J. S.'s mother and grandmother and by the natural course of his disease. Rothmund's Syndrome[12] and Werner's Syndrome[13] were eliminated by the lack of both sweat glands and cataracts. The presence of eczema and wheezing, as in our patient, has been noted before[14] and may result from increased permeability due to hyperplastic changes in the respiratory mucosa.[15]

The accepted mode of inheritance of HED is in a single x-linked recessive pattern.[16] Since fully expressed HED has been reported in females,[17] alternate inheritance patterns have been postulated among which are an autosomal recessive where consanguinity can be shown[18] and a new mutation to explain the sporadic cases in females. The full expression in females has also been approached by the Lyon hypothesis[19] which assumes near total inactivation of the normal X chromosome. An autosomal dominant[20] and an X-linked dominant[21] have also been postulated. It seems possible that each of the above has been operative in some of the reported families. Thus, since no one explanation served to explain all the cases, it is likely that we are dealing with a situation of genetic heterogeneity. In our patient it is probable that the mode of inheritance is sex-linked recessive.

The demise of Mrs. S.'s second child within fifteen minutes of birth is apt to be unrelated to HED. Mrs. S.'s male sibling died at an early age and there was no information available concerning this child. Since the characteristics of HED may not be manifest until almost one year of age, speculation concerning these two infants is not tenable.

HED is a disease for which no cure is now known. Although treatment is symptomatic and supportive, it has proven of value in both the physical and emotional well-being of the affected individual. Consequent to the lack of sweat glands temperature control may become a problem. Older individuals learn heat avoidance and employ wet applications to their bodies to deal with temperature regulation. In infancy this is a more serious problem and failure to establish a correct diagnosis may result in permanent neurological impairment, secondary to hyperpyrexia. Indeed, hyperpyrexia due to HED has been reported in the neonatal period.[22]

Hypodontia and hypotrichosis, although not life-threatening, are important considerations in the management of HED. Although hypodontia does not lead to impaired development of the facial and jaw bones,[23] its importance lies in cosmetic deformity, speech impairment, faulty mastication and probability of affective disorder. Our patient, a good example of these non life-threatening sequellae, presented with possible mental retardation, disturbed verbal communication and autistic-like behavior. Hypotrichosis, frontal bossing, pointed chin and saddle nose deformity contributing to a sunken dishpan face resulted in his being ridiculed by others. From the above discussion, it is evident that psychological problems can ensue and, of course, have been previously reported.[24]

Treatment of HED consists of dealing with temperature control, counseling or therapy for family and/or patient, teacher counseling, speech

TABLE 1: Number of sweat pores per centimeter in selected areas of J.S., his mother and his brother.

	Sibling		Mother		Proband	
	R	L	R	L	R	L
Tip of third finger	25	25	15	20	3	7
Second interdigital space	21	22	+*	11	2	0
Area between transverse flexion crease	23	29	+	+	3	2
Hypothenar area	23	17	+	15	0	4
Thenar area	19	24	13	13	0	0

* Those areas designated with "+" were so irregular that a count along a single dermal ridge was not possible.

therapy, dentures which must be redesigned with jaw growth and a wig if emotionally and/or cosmetically indicated. The patient received all of the above and has made considerable progress in learning to deal with his problem.

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Economic Aspects of Drug Over Use*

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This paper endeavors to assess selected economic factors that may be associated with the over use of drugs in the American society. In attempting to analyze our problem, we are confronted immediately with the twin hurdles of concept and measurement. Both issues are significant and neither is susceptible to simple interpretation. Indeed, it would probably be difficult to find a topic for discussion that is more elusive. Consequently, further work is required in many instances before conclusions can be drawn.

Conceptual and Methodological Limitations

It seems to be acknowledged generally that a drug is any substance that has any physiological or psychological effect on living tissue. While this definition may be germane for examining a broad range of questions concerning human response and related social policies, it is too comprehensive for our purposes here. Thus we are forced to put aside important questions regarding how personal health is influenced by the use of alcohol, nicotine, caffeine and food. In a similar fashion, we must exclude very significant problems of indirect consumption present in the form of food additives, the routine use of pharmaceuticals to enhance the commercial sale of animal products, and the application of pesticides to facilitate crop development.[1] Moreover, we will also by-pass the critical issues of environmental and industrial pollution. (To the extent that such factors impair an individual's health, he may subsequently become a direct consumer of drug products in order to help control his medical condition.)

This delimitation will enable us to focus on three major components of the drug problem. The first involves the utilization of legend pharmaceuticals. These products are those designated by law as requiring the order of an authorized prescriber before dispensing can legally take place. A number of these agents, some 28 of the 200 sold most frequently, have been defined as especially dangerous and are subject to further restrictions under the Controlled Substances Act.

The second component covers over-the-counter drug products. These items are pharmaceutical preparations usually subject to the labeling requirements of FDA but excluding legend products. In considering this area of OTC preparations, we are faced with a number of difficulties such as accepting an official determination that an item is indeed a drug, monitoring products that are characterized by a relatively rapid entry into or exit from the marketplace, and obtaining accurate estimates of retail sales.

Our final drug category includes the utilization of inhalants, hallucinogens, cannabis, and similar illicit or illegal substances. If we wish to examine the larger issue of psychological or physical dependence, the third category must be expanded further to reflect the use of certain abused products such as barbiturates, amphetamines, and related items normally included in the classifications noted previously.

When the three basic drug categories —legend, OTC, and illicit—are combined, we find that total market sales exceeded 13 billion dollars in 1972. This sum is comprised of \$9.3 billion representing the use of prescription drugs and approximately two billion for over-the-counter products.[2] The residual, about two billion, is a rough estimate of the minimum figure attributable to the value of street sales for abused substances. Since the commercial basis for such transactions is very informal, measurement of any economic implications might be more successful if an attempt is made to record factors such as governmental outlays for regulation and treatment, losses in productivity and so forth. The economic impact of an over drugged community, of course, is not confined to direct market sales and labor force participation.

A traditional economic view of our problem would give considerable attention to the questions of how resource allocation was influenced by the nature of market controls, the extent of monopolistic pricing, the level of profits enjoyed by manufacturers and retailers, and so on.[3] Even if all prescribing, dispensing and drug use conformed closely to the parameters of official labeling and supporting standards developed by professional experts, these basic issues would remain. However, since this discussion is directed toward the economic ramifications of an over drugged society, such questions will be excluded unless particular products are used beyond the pale of scientific indication.

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The task of measuring and interpreting various economic dimensions is impeded by a number of factors. (1) Some of the more critical problems in drug usages are dynamic—witness the changing pattern of abuse as we have experienced cycles of heroin, methadone, tranquilizer and amphetamine consumption. By the time economic and social aspects of a given problem are perceived, the fundamental characteristics may have changed significantly.

(2) Our understanding of drug usage problems may be influenced by definitional rigidities. For example, if an individual alternates his consumption between alcohol and drugs, the values perceived by the economic model defined above will fall or rise accordingly. The underlying problem of personal behavior and adjustment, however, may be subject to a much smaller degree of variability.

Moreover, if our analytical model is restricted to the direct and indirect expenditures for drugs, it will mirror activities within that frame of reference. However, if we are interested ultimately in minimizing the total cost of a given illness, other factors must be considered. For example, when novobiocin is indicated, hepatic and hematological studies should be made routinely during treatment.[4] If these tests are not carried out (and accurate results received by the physician), patient response may not be successful and the medication may be wasted. In certain instances, therefore, it will be necessary to define and study total procedures and aggregate costs associated with an episode of care.

(3) Although the overall output of legal pharmaceutical production can be measured with some accuracy through the activities of governmental regulatory agencies, national estimates covering utilization statistics for prescribing, dispensing and illicit or illegal drug use are either non-existent or restricted to ad hoc surveys. In addition, because business firms at both the producer and retailer level market more than one product, segregation of costs and profits for pharmaceuticals is a tenuous exercise.

(4) Drug purchase and possession is not necessarily synonomous with drug consumption. Household surveys of medicine chest inventories usually show significant quantities of unused medications being maintained by a typical family. If the patient terminated ingestion because the drug was directly responsible for his recovery, we have identified one type of problem for study. If, however, the residual supply was due to inappropriate prescribing, including the purchase of an "ineffective" product, we have an economic issue with different characteristics.

(5) If a pharmaceutical producer marketed a product with prior knowledge of its ineffectiveness or lack of safety, or refused to conduct adequate clinical trials to establish the agent's therapeutic value, it is necessary to calculate the cost of economic resources dissipated in all such ventures. If, on the other hand, adequate clinical trials yielded sufficient evidence to warrant FDA approval of a new product, but subsequently toxic side-effects are perceived that could not have been predicted except after extended use, economic costs here would have to be recorded as a necessary expense of scientific progress. MER-29 might be cited as representative of the former category and chlorpromazine or diphenlhydantoin as falling into the latter.

(6) Prescribing decisions may be influenced by bona fide variations in professional interpretation regarding appropriate therapy. An evaluation of drug selection, therefore, would have to devote some attention to the severity of the patient's condition, his capacity to "function in daily tasks and roles if unmedicated, the risk of side effects, the probability of success, and the practical availability of alternative therapies."[5] In short, economic appraisal is dependent upon prerequisites in the form of scientific and professional standards regarding drug utility and sound therapy.

(7) The quality of prescribing decisions is influenced partially by drug information furnished or supported by industry, professional and government sources. One position might argue that current responsibilities and expenditures for this function, including the resultant patterns of drug utilization, should be maintained without major modification. Another view, would contend that annual savings of over $800 million could be effected if society would undertake the development of a more systematic and rational communication system. Moreover, improved patterns of prescribing and patient response stemming from this step probably would yield additional savings equal to or greater than the primary figure. The amount of these direct and indirect savings, though, is subject to a number of assumptions covering both theory and practicality.

This enumeration of methodological hazards is incomplete but it may be more useful to turn now to the matter of inappropriate drug use when a medical basis for intervention is present.

Medical Necessity and Inappropriate Use

Perhaps the most obvious illustration of an economic issue is found in the withdrawal of 339 New Drug

Applications by the Food and Drug Administration. This action was necessary because scientific review found that these agents were "ineffective." Their combined annual sales volume is estimated to have been $155 million.[6] If the basis for analysis is shifted to actual product life, this sum will rise considerably. A similar problem appeared when a sample of some 420 important OTC drug products was studied. Preliminary findings indicated that only 25 percent were "effective."[7] When the tentative classifications of "probably" and "possibly" effective are resolved for both legend and OTC items, the category with major economic significance, "ineffective" drug products, undoubtedly will increase further.

Another problem is manifest in the particular area of analgesic products sold over-the-counter. In 1969, this market totaled nearly $560 million but about $360 million of that amount was accounted for by the purchase of combination products. Most of these items, according to one expert,[8] are pharmacologically and therapeutically as well as economically irrational. In the same year, though, this problem was dwarfed by the consumption of OTC remedies for coughs and colds worth approximately $900 million.[9] Turning to the role of legend drugs, we note that about 12% of all prescriptions, mostly in the form of antibiotics, are given to counter-act the common cold. These patterns of utilization persist despite the concurrence of expert opinion that "there is no available chemotherapeutic or antibiotic agent effective against the numerous viruses that may cause the common cold syndrome."[10] Even though patient judgment or pressure may contribute importantly to such results, the economic consequences are still negative.

The classic example of inappropriate drug use, and hence economic waste, is found in the case of chloramphenicol where nearly 700,000 persons annually are exposed to a very toxic drug for non-indicated reasons.[11] Moreover, several formal studies appraising the use of antibiotics in hospitals corraborate that about 30% of the patients were given such medications despite the fact that nearly two-thirds of such individuals never had documented infections.[12]

Our general problem is not confined to hospital prescribing. "In fiscal 1972, FDA certified about 2,400,000 kilograms of the eight most commonly used antibiotics. This would amount to 50 doses of an antibiotic for every man, woman and child in this country per year or enough to treat two illnesses of average duration . . . yet it is doubtful if the average person has an illness that requires treatment with an antibiotic more often than once every five or ten years."[13] On the other hand, we find that many "physicians prescribing antimicrobial drugs use inadequate dosage or fail to use them at all."[14] Although this example does not fit in the category of over use, any under use of prescription agents has economic consequences that are just as real as our subject for discussion.

When we turn to the matter of adverse drug reactions involving patients hospitalized on the medical service, we find that the annual cost of institutional care due to this cause ranges from $3.0[15] to $3.6 billion.[16] In addition to the morbidity factor, there are nearly 30,000 deaths per year that can be attributed to adverse reactions. The economic loss of premature death can be calculated by adjusting expected future earnings of the deceased. But in undertaking such an exercise, one should not overlook that fact that from 70 to 80% of the adverse reactions are predictable and therefore could have been prevented. The economic cost of these preventable deaths can be estimated at nearly two billion dollars a year. If one also calculates the institutional cost of treating patients subject to preventable adverse drug reactions, an additional national outlay of more than two billion dollars can be identified.[17] These simple calculations demonstrate that society could spend up to four billion dollars annually before control techniques no longer would be cost effective. Since many other potential savings in drug use are apparent, four billion may be regarded as a minimum estimate.

One of the most certain and efficient mechanisms for dealing with the problem of excessive drug use is the development of a national health care information system. Given the installation of advanced electronic terminals in the offices of prescribers and dispensers, information on prescribed and perhaps OTC drugs[18] could be captured effectively. With the use of regional computer data banks, predictable drug interactions and many patient-drug reactions could be controlled through professional interface with such a system. Moreover, this comprehensive information network could probably be operated for well under a billion dollars per year. In light of a favorable cost-effectiveness ratio of at least four to one, coupled with the added benefit of being able to handle all personal and third-party health insurance records without any increase in real economic cost, it appears that the possible parameters of such a system merit the close attention of American physicians and pharmacists as well as Federal officials responsible for drug use and health care policy.

Despite the apparent economic advantages of an information network, the computer has limited capability for ensuring that patients take their medication as appropriate. According to a number of studies, "the percent of patients making errors in the self-administration of prescribed medications, with few exceptions, has ranged between 25 and 59 percent."[19] Since this situation is affected by both the nature of professional instructions and patient compliance, among others, a remedial program will have to deal with a number of factors. Regardless of the source, errors in self-administration of both legend and non-legend items contribute to a given level of cost associated with the use and over use of drugs.

Drug Use with Questionable Therapeutic Value

The foregoing analysis of prescribed drugs assumed that the patient's condition required some form of professional intervention. Thus it concentrated on selected problems that seem to fall clearly within the domain of excessive drug use. The more popular interpretation of an over drugged society, however, usually reflects concern over the ingestion of agents where the medical basis is more questionable or even non-existent. Given such circumstances, economic evaluation is more difficult. There are, however, several points that warrant consideration in reviewing the use of pharmaceuticals under questionable conditions.

In the prescribing of psychotropic agents for outpatients, a significant proportion of such use apparently is designed to improve social functioning or help the individual overcome the ordinary problems of living. One expert has observed that if society feels that "the enhancement of normal performance is a legitimate use of drugs," then such utilization would be considered legitimate.[20] All other things being equal, this position can be supported as an essential component of a free society. However, a number of prior conditions would have to be fulfilled. (1) If the physician believes that the patient would be treated best with a placebo, the least expensive alternative ought to be prescribed in lieu of a more expensive agent. If patient response is predicated on the knowledge that a high-priced substance was being ingested, private purchase of low-cost agents will make it difficult to convey this impression. Under drug insurance though, it might be possible to dispense minimum cost substances but let the patient understand that the product's value was much greater.

(2) Both the prescribing of psychotropic medications and patient demand for them are associated with promotional efforts carried out by large pharmaceutical manufacturers to sell their wares. In short, society's approval of expanded drug use is not an independent reflection of patient need and professional judgment, but one that has been contrived through persuasive campaigns to stimulate the use of drugs in dealing with nebulous symptoms such as "environmental depression," "behavioral drift," and so forth. Until the role of these intervening variables is terminated, it would be hazardous and costly to rely on societal sanction as a basis for approving drug use.

(3) The action of psychoactive medications tends to be less specific and more diffuse than that of other drugs in the physician's arsenal. As a result, they tend to elicit a broader range of unintended and unanticipated side effects, consequences or costs than do other drugs.[21] Moreover, since the absolute lack of toxicity is an impossibility,[22] the economic fall out related to utilization of psychotropics could be considerable whenever they are prescribed beyond the limits indicated in official labeling.

Drug Use without Medical Justification

In attempting to measure the economic aspects of drug use without medical justification, we are again confronted with the iceberg problem. The simplest type of expenditure to isolate is found in the allocation of Federal funds to various functions that deal with drug abuse. In the year ending June 30, 1972, some $460 million was expended for this purpose while the fiscal 1974 budget calls for an outlay of nearly $720 million. Indeed, the National Commission on Marijuana and Drug Abuse recently noted that the government is a short step away from creating an institutionalized billion-dollar drug abuse industrial complex.[23]

There are a number of events related to our basic problem where expenditures will not necessarily be enumerated in a typical accounting of drug abuse costs. Illustrative activities that might be excluded inadvertently are as follows:

> Twenty-one states provide specialized drug treatment for imprisoned drug offenders.[24]
>
> Twenty-four states have instituted compulsory drug education programs in their public schools.[25]
>
> There are at least 133 national professional, law enforcement, government, youth and service groups operating to "find rational approaches to drug abuse prevention." (These agencies are members of the National Coordinating Council on Drug Education.)
>
> Formal and informal meetings are continuously being held to discuss issues related to drug abuse. (The registration fee alone was $20 to attend the Fifth National Conference On Methadone Treatment.)
>
> The rapid rise in the burglary rate of community pharmacies as drug users seek supplies to support their habit.
>
> Resources are consumed in deliberations conducted by legislative bodies. For example, in the 93rd Congress, at least 12 bills have been introduced in the House of Representatives to deal with various aspects of drug abuse.

> Even if treatment is successful, social barriers may perpetuate our economic costs. For example, 30,000 out of the 50,000 recovered drug addicts in New York City have been unable to obtain employment because they are considered extreme risks.[26]
>
> Resources deployed to combat the problem may be wasted: Witness the National Coordinating Council assessment that 84 percent of the drug abuse education films and audiovisual materials are either grossly inaccurate, misleading or unclear.

These examples should be sufficient to demonstrate that an economic appraisal of drug abuse in our society is a complex task. In undertaking such an analysis, one should not overlook the likelihood that the most salient economic parameter undoubtedly will prove to be the most difficult to measure and overcome. We refer here to the long-term social costs in human reclamation that appear when serious abuse occurs. The fact that our nation now has clinical facilities to formally treat some 200,000 individuals annually is an index of future problems that may emanate from the current attitude of fly now-pay later.

Discussion

There are some additional economic and institutional factors that should be considered in any attempt to develop meaningful controls for an over drugged society:

> The exclusion of drug coverage under insurance programs for ambulatory patients may have certain uneconomic results: (a) hospitalization rates may increase for individuals who lack necessary funds to purchase needed medications; (b) institutions may provide patients with excessive drug supplies when they are discharged if only inpatient coverage is provided; (c) without a data base, it is difficult to implement a quality assurance program.
>
> The change in personal attitudes in that "people demand relief and expect relief to a greater extent and are willing to tolerate discomfort to a lesser extent than they were 35 years ago."[27]
>
> The absence of a compensation system and other mechanisms for dispensers that would induce them to evaluate drug purchases more carefully in terms of sound therapeutic criteria.
>
> The reluctance of drug specialists (physicians, pharmacists, and clinical pharmacologists) to promulgate scientific standards for appropriate drug use and implement review procedures to ensure their enforcement. Recent legislation authorizing the establishment of Professional Standards Review Organizations provides an opportunity to remedy this deficiency.
>
> The failure of society to make a sharp distinction in public policy between the moral, medical, and criminal basis related to drug abuse. Moral problems (recreational pharmacology) are often treated as criminal matters while certain criminal cases may be subject more logically to medical interpretation. As a consequence, the economic results of drug use are not independent of cultural values and government action.

While these and other variables merit further attention, progress may be dependent upon overcoming an even more basic constraint. It seems that individuals and society often have a proclivity to respond more to symptoms than underlying causes. Until our nation can find a formula for making life in general more purposeful, productive and humane, we must anticipate that certain forms of drug use and abuse will continually be invoked to fill that void.

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ECG Problems

(from page 598)

INTERPRETATION:

1. Paroxysmal atrial tachycardia with block and irregular A-V conduction.
2. Left axis shift (–40°).
3. ST-T changes of digitalis effect.

The atrial rate is 240 per minute as measured in V_1 with the ventricular rate averaging about 120. It is characteristic of this arrhythmia that the P waves are clearly identifiable as such and do not represent simple undulations or sawtooth aberrations of the baseline. This rhythm is frequently caused by digitalis and may be a sign of digitalis toxicity, particularly in the presence of low serum potassium. The atrial rate is characteristically between 150 and 250 per minute, and there is A-V block of 2:1 or more. It is difficult to distinguish this rhythm from atrial flutter, particularly when the atrial rate is relatively fast. In flutter, however, the atrial rate is usually 250 to 350, and the atrial activity is more characteristically "sawtooth" in contour without such well structured P waves. The major importance in differentiating these two rhythms lies in the recognition that PAT with block is often a digitalis produced arrhythmia.

Edited by Robert R. Montgomery, M.D.

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Warnings: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Warn patients of possible additive effects with alcohol and other CNS depressants.
Usage in Pregnancy: In pregnancy, nursing mothers and women who might bear children, weigh potential benefits against hazards. Inhibition of lactation may occur.
Effect on PBI Determination and I^{131} Uptake: Isopropamide iodide may alter PBI test results and will suppress I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.
Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.
Adverse Reactions: Drowsiness, excessive dryness of nose, throat or mouth; nervousness; or insomnia. Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).
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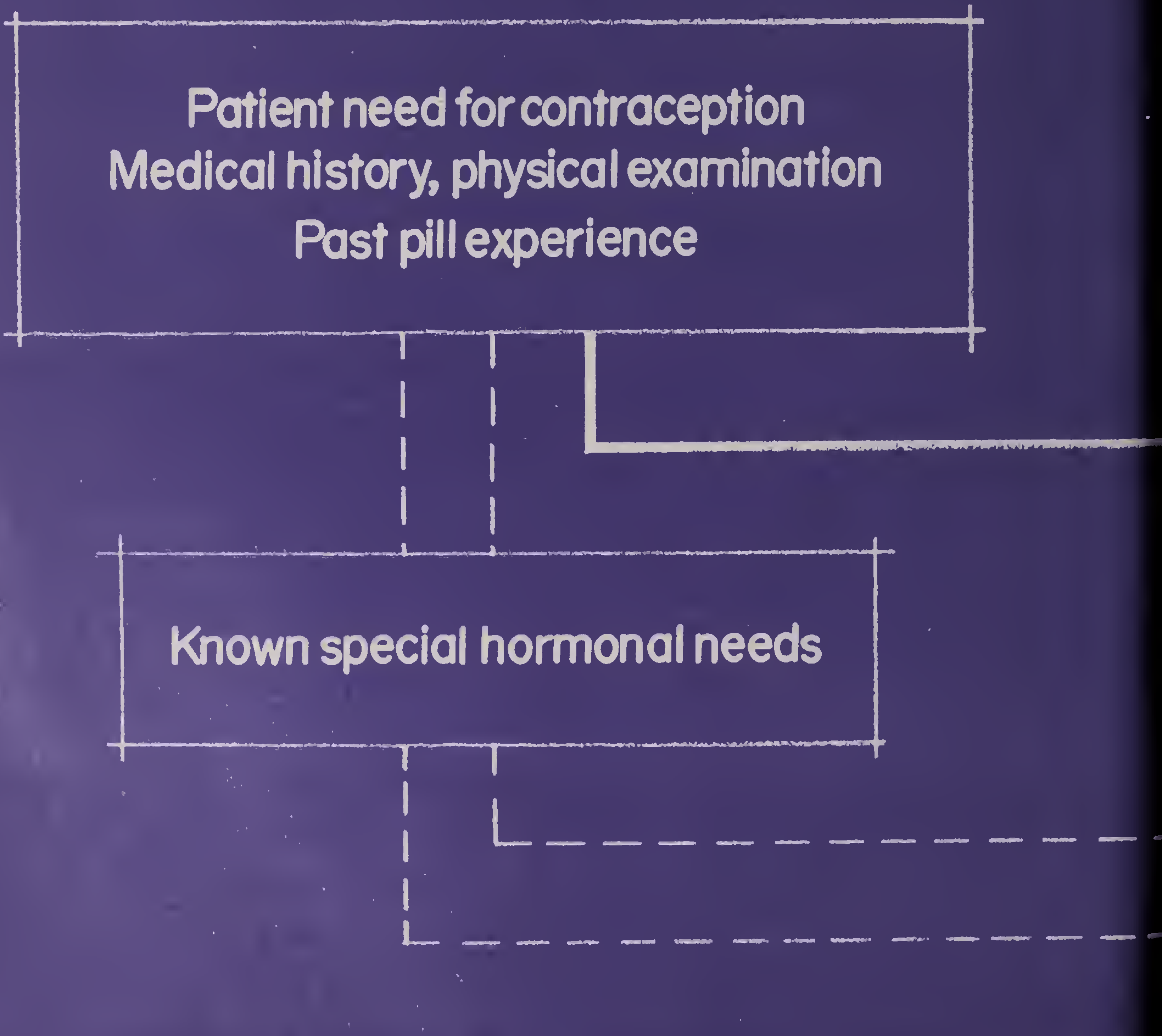

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primarily on animal studies.

Note: Oral contraceptives are complex medications. As with all medications they should be prescribed with discriminating care, and only after reference to full prescribing information. For brief summary of prescribing information, please see next page.

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Actions—Ovulen and Demulen act to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen and Demulen depress the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note—Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen and Demulen are indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality conducted in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in the United States. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen and Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen or Demulen. Therefore, if such tests are abnormal in a patient taking Ovulen or Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen or Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen or Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen or Demulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen or Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967. **2.** Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199 (April 27) 1968. **3.** Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657 (June 14) 1969. **4.** Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Amer. J. Epidem. *90*:365-380 (Nov.) 1969.

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Indication—Enovid-E is indicated for oral contraception.

The *Special Note, Contraindications, Warnings, Precautions* and *Adverse Reactions* listed above for Ovulen and Demulen are applicable to Enovid-E and should be observed when prescribing Enovid-E.

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MEMBERSHIP COMMITTEE

Duties and Functions

1. The Membership Committee, as a standing Committee of the Medical Society of the District of Columbia, has various duties and functions which relate primarily to the recruitment of new members. In the area of recruitment, considerable attention is given to the following categories:

A. Newly licensed physicians
B. Medical students
C. Residents and Interns

The D.C. Licensure Commission furnishes the Society, on a regular basis, a list of all M.D.'s who have been newly licensed to practice medicine in the District of Columbia. Each of these persons is mailed a special packet of information, including a membership application, and asked to consider becoming a member of the Society.

Also, on an annual basis, the Membership Committee, through an extensive mailing, invites area Residents and Interns and medical students to become members of the Medical Society of the District of Columbia.

2. The recruitment of new members is the most important function of this Committee, however, there are other activities which come under its purview. These include:

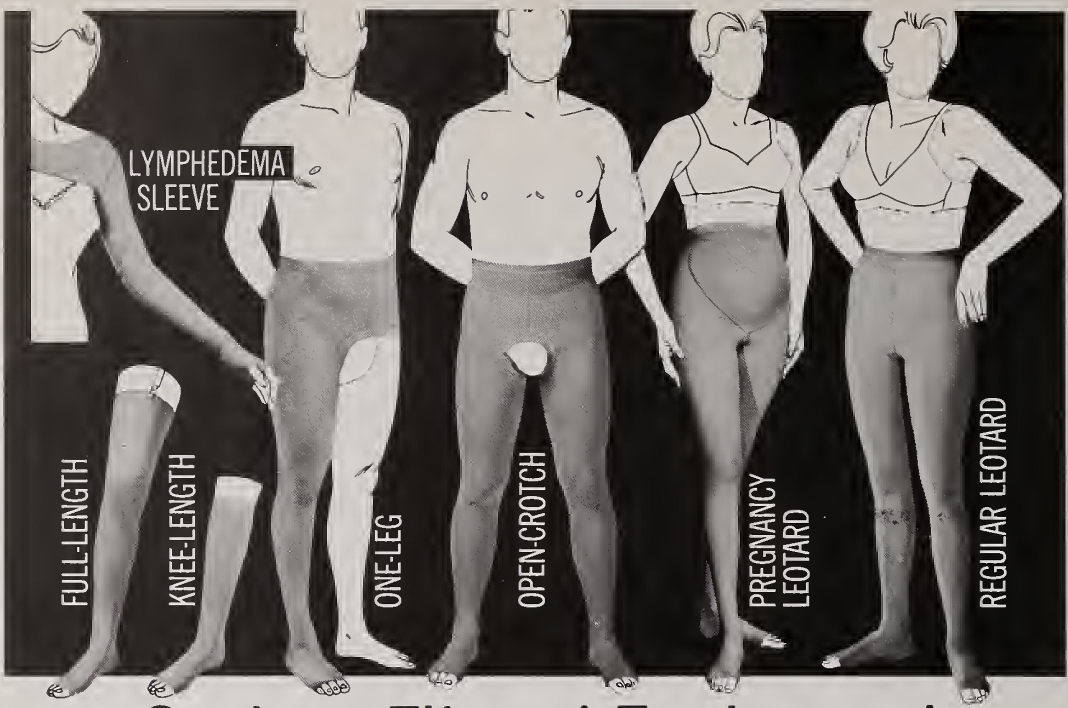
A. *Sympathy Assignment Calender*—Upon the death of a member of the Society (Active Life or Special member) a member of the Membership Committee, on behalf of the Society, will visit the funeral home and/or family of the deceased. Flowers are sent by the Society to the funeral home. Members of the Membership Committee perform this function on a rotational basis.

B. *Quarterly Reception for New Members*—Approximately every three months, the Committee hosts a special reception for all new Society members and their spouse. The occasion allows new members to meet and talk with the officers of the Society and also allows the wives an opportunity to talk with members of the Women's Auxiliary.

C. *Endorsement of New Members*—The Society's Constitution and Bylaws require that all new members must have the written endorsement of three Active members of our Society, other than members of the Board of Credentials or the Executive Board. Quite often, physicians who are new to the area do not know three Active Society members. The Membership Committee fulfills this need by inviting the prospective member to attend one of its monthly meetings and, following the interview of the applicant, members of the Committee will provide the endorsements.

D. *Honorary Members*—On an annual basis, the Membership Committee reviews the list of Honorary Society members, and through a questionnaire mailing process, is able to keep this category of membership current. The Membership Committee also will consider, review and recommend to the Board of Credentials any prospective new candidates for Honorary Membership status.

E. *Financial Help*—On occasion, the Society will receive a request from, or become aware of, a member who is in financial distress. The Committee may be called upon to review the request and forward its recommendation to the "Ruffin Fund" Committee, which makes final determination as to loans or gifts to needy physicians.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NEW MEMBERS

Active

MARY G. BEALE, M.D. Office: 4040 51st Street, N.W. Born in Washington, D.C. Medical degree: Johns Hopkins, 1970. Specialty: Pediatrics.

ILNES BEAUMONT-HINDS, M.D. Office: 1707 7th Street, N.W. Born in Jamaica, West Indies, Medical degree: Howard University, 1966. Specialty: Pediatrics.

JEROME BLOCK, M.D. Office: 9000 Rockville Pike, Bethesda, Maryland. Born in New York, New York. Medical degree: New York University, 1956. Specialty: Internal Medicine–Oncology.

SIDNEY ECKER, M.D. Office: 50 W. Edmonston Drive, Rockville, Maryland. Born in Scranton, Pennsylvania. Medical degree: Albert Einstein University, 1966. Specialty: Urology.

RICHARD N. EDELSON, M.D. Office: 2141 K Street, N.W. Born in New York, New York. Medical degree: Harvard Medical School, 1966. Specialty: Neurology.

STEPHEN ETTENSON, M.D. Office: 2141 K Street, N.W. Born in New York, New York. Medical degree: George Washington University, 1966. Specialty: Psychiatry.

WADIE FAM, M.D. Office: Freedmen's Hospital. Born in Luxor, Egypt. Medical degree: College of Medicine, Cairo University, 1956. Specialty: Internal Medicine–Cardiology.

EDWARD S. FLEMING, M.D. Office: 1825 K Street, N.W. Born in San Diego, California. Medical degree: George Washington University, 1957. Specialty: Psychiatry.

ALLEN GINSBERG, M.D. Office: 2150 Pennsylvania Avenue, N.W. Born in New York, New York. Medical degree: Johns Hopkins, 1966. Specialty: Gastroenterology.

LUCIE GOMEZ, M.D. Office: 5321 Macomb Street, N.W. Born in Cali, Colombia, South America. Medical degree: Emory University, 1960. Specialty: Internal Medicine–Cardiology.

GHASSAN JWEIED, M.D. Office: Providence Hopsital. Born in Ajulun, Jordan. Medical degree: Cairo University, 1962. Specialty: General Surgery.

NATIVIDAD LERUM, M.D. Office: Rogers Memorial Hospital. Born in the Philippines. Medical degree: Far Eastern University (the Philippines), 1960. Specialty: General Practice–Emergency Room.

SURESH LIMAYE, M.D. Office: Georgetown Hospital. Born in Jamkhundi, India. Medical degree: T. N. Medical College, Bombay, 1961. Specialty: Ophthalmology.

JOHN W. MELTON, M.D. Office: 1234 19th Street, N.W. Born in Richmond, Virginia. Medical degree: Medical College of Virginia, 1967. Specialty: Internal Medicine–Rheumatology.

THOMAS J. NEVIASER, M.D. Office: 2430 Pennsylvania Avenue, N.W. Born in Washington, D.C. Medical degree: George Washington University, 1966. Specialty: Orthopedic Surgery.

ARTHUR SCHWARTZ, M.D. Office: 5454 Wisconsin Avenue. Born in New York, New York. Medical degree: Albert Einstein University, 1968. Specialty: Ophthalmology.

RAMAKANT SHAH, M.D. Office: Freedmen's Hospital. Born in Ahmedabad, India. Medical degree: B. J. Medical College (India), 1966. Specialty: Internal Medicine–Cardiology.

HAROLD SHELBY, M.D. Office: D.C. General Hospital. Born in Rockford, Illinois. Medical degree: Howard University, 1969. Specialty: Gastroenterology.

JACK B. TAYLOR, M.D. Office: 2150 Pennsylvania Avenue, N.W. Born in Smithfield, North Carolina. Medical degree: Duke University, 1965. Specialty: Internal Medicine–Cardiology.

STEVEN J. WOLIN, M.D. Office: 5225 Connecticut Avenue, N.W. Born in New York, New York. Medical degree: Albert Einstein University, 1966. Specialty: Psychiatry.

Associate

RAMESH DESAI, M.D. Office: Freedmen's Hospital and D.C. General Hospital. Born in Dohad, India. Medical degree: Baroda Medical College (India), 1965. Specialty: Internal Medicine–Gastroenterology.

Resident-Intern

CHARLES BIER, M.D. Office: George Washington University Hospital. Born in Washington, D.C. Medical degree: George Washington University, 1968. Specialty: Internal Medicine.

DAVID CURFMAN, M.D. Office: George Washington University Hospital. Born in Bucyrus, Ohio. Medical degree: George Washington University, 1973. Intern.

DENIS HARRIS, M.D. Office: George Washington University Hospital. Born in Milwaukee, Wisconsin. Medical degree: University of Wisconsin, 1972. Specialty: Orthopedic Surgery.

MARSHALL NICKERSON, M.D. Office: Freedmen's Hospital. Born in Toledo, Ohio. Medical degree: Howard University, 1972. Specialty: General Practice.

VERNON C. SMITH, M.D. Office: Freedmen's Hospital. Born in Atlanta, Georgia. Medical degree: Howard University, 1972. Specialty: Family Practice.

MARIJA SMOKVINA, M.D. Office: George Washington University. Born in Kranj, Yugoslavia. Medical degree: University of Ljubljana (Yugoslavia), 1959. Specialty: Physical Medicine and Rehabilitation.

Transfers

Active to Associate: Peter Oberhoff, M.D.

Resident-Intern to Active: Owen Dillon, M.D., Suresh Goyal, M.D., David Notes, M.D.

Resignations

Active: Brian Blades, M.D., John R. Lilly, M.D.

A Handicapped Child in the Family. VERDA HEISLER, PH.D. Price, $7.95. Pp. 160. New York: Grune & Stratton, 1971.

There are many unresolved inner conflicts and feelings in the minds of parents of handicapped children. The energy from these unresolved conflicts will summate up from repetitive experiences within the parent and cause many emotional symptoms manifestly in the parent who suppresses or represses these thoughts within themselves. The parent may go through stages of shock, denial of the injury or illness of the handicapped, and depression in his attempt to adapt in a healthy way to the constant stress of dealing with his child's disability. Non-verbalized anxieties may cause the parent to be evasive, to avoid, to disturb the normal parent-child relationship, and to feel guilt and resentment about the role he must play as parent of his own children.

Dr. Heisler directs the contents of this book to those parents who have children with either mental, emotional or physical disabilities. She quickly points out, however, that this book is not an easy how-to-do-it solution to the problems faced, but that it is a book pointing out the process which parents should go through as they attempt to have and attain conflict resolution about their role relationship with their children. Dr. Heisler's expertise emanates from her full-time private practice as a consultant psychologist since 1951, devoting most of her time to individual and group psychotherapy with adults. She also has the knowledge and personal experience of overcoming the severe physical impairment of childhood polio and she utilizes the termination of these experiences in her broad approach in assisting the parents of the handicapped child. The format for learning how to resolve the inner conflicts takes place in a group psychotherapy with parents of handicapped children. Through the group process the parents are capable of verbally discharging some of their inner thoughts and feelings about their own inability or hesitancy to make overprotecting or giving time and attention to the demands and needs of the handicapped child in the family. There is also much social guilt brought about by the awareness of the child's potential problems and fitting into the social concepts of acceptance by his peers and by other family members. Frequently, the parents have only communicated their feelings about having a handicapped child in the family to a selected few and the ability to communicate with each other begins the process of resolving many inner conflicts about being parents of this child.

Dr. Heisler continues by explaining the group interaction in her sessions with the parents. She brings out the importance of the early years of life in the formation of the personality of the child and allows the parents to feel a greater sense of adequate responsibility as individuals as they relate to their children. The process is one of catharsis, as we see in many psychoanalytically-directed group therapy sessions. Many questions become answered to the satisfaction and comfort of both parents and other members of the family, all of whom are attempting to delineate their identity role as members of the family. Physical and psychosocial and psychosexual adjustments are readily discussed in such a way that there is a healthy process development which allows each member of the family to feel an integral part of the system in growing up together. In a less psychoanalytic approach, but in an extremely important supportive therapeutic approach, the author utilizes her own experiences to demonstrate how one goes about resolving the inner conflicts of meeting the challenges of everyday life. The parents in this group found it comforting to share their feelings with other parents with whom they had the common bond of a handicapped child and, in the process, the communication between these parents soon began to open up into other areas of their lives and allowed for growth and development of the parents as individuals, which, in turn, increased their ability to relate to the handicapped member of the family.

The author states that the contents of the book are designed to help a specific portion of the population, namely the parents of handicapped children, but this book is very useful to all workers to assist them and make them aware that group psychotherapeutic processes are extremely useful as a therapeutic tool to produce optimal functioning and healthy adaptative mechanisms for coping with life.

W. G. TOMPKINS, M.D.

Non-Human Primates and Medical Research. GEOFFREY H. BOURNE, Editor. Price, $25.00. Pp. 537. New York: Academic Press, 1973.

This monograph conceived by the Director of the Yerkes Regional Primate Center in Atlanta, Georgia brings together the varied applications of the Non-Human Primate in medical science. Each of the first 21 chapters presents a detailed literature review of a specific application written by an expert in that particular area of application and includes a summation with thoughts on future application. The final chapter is an historical description of the Primate research program in the U.S. While this volume will find little use on the bookshelf of the practicing physician, it's presence in a reference library would be extremely useful as a source of excellent information on primate physiology and the place of the non-human primate in the study of human disease.

NORMAN C. KRAMER, M.D.

Alcohol & Health. REPORT FROM THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE. Price, $3.95. Pp. 372. New York: Charles Scribner's Sons, 1973.

It is not often that a physician can find an excellently prepared book to which he can turn for important data. The monograph "Alcohol & Health" is an extremely thorough review of the various medical aspects of alcoholism. In addition to statistics, it gives a well-structured and organized historical, theoretical, pharmacological and legal treatise on the subject. The monograph is excellently referenced and indexed, easily read, and a mandatory addition to any interested person's library on the topic of alcohol. Unlike many other medically related books, "Alcohol & Health" can be and should be read by any interested party be they laity, scientist or alcohol addict.

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Progress in Neurology and Psychiatry, Vol. 27. E. A. SPIEGEL, M. D., Editor. Price, $26.50. Pp. 372. New York: Grune & Stratton, 1973.

The information explosion in medicine, as in other academic fields, makes it essential that good reviews and progress reports be available, to enable one to keep up to date in his field. *Progress in Neurology and Psychiatry, Vol. 27*, edited by E. A. Spiegel, might be expected to fill such role; it calls itself "an annual review," and is divided neatly into four sections labeled Basic Sciences, Neurology, Neurosurgery, and Psychiatry. Unfortunately, however, the book is little more than a gigantic listing of references, telling what subject the articles are about, but often giving none of the important information. Even when conclusions are given they are often too vague to be really helpful. For example, "Angiomas may be successfully treated with embolization of steel spheres." No further comments are made for that provocative statement.

The volume will be useful for the investigator who wants simply the references so that he can read the original article; the number of references is immense—well over 100 each for almost all of the 22 chapters. But the person interested in a pleasant, feasible way to bring himself up to date on what he might have missed the preceding year will find little use for this book.

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Frontiers in Comparative Medicine, Vol. 1, No. 1: THE WESLEY W. SPINK LECTURES ON COMPARATIVE MEDICINE. W. I. B. BEVERIDGE. Price, $4.75. Pp. 104. Minneapolis: University of Minnesota Press, 1972.

This book is the first of a series of lectures dedicated to Wesley W. Spink for his contributions to Medicine and Infectious Diseases. The choice of Comparative Medicine reflects Dr. Spink's studies of Brucellosis in man and in other animal species. By crossing artificial boundaries of various disciplines of science and medicine he added new information which is of benefit to man and animals.

Professor Beveridge, from the School of Veterinary Medicine in Cambridge, England, presented three lectures. In the first, on the logic of the comparative method, he points out the rationale for research based on analogy between disease in man and disease in the rest of the animal kingdom. Although data obtained from animals cannot be applied directly to the human problem, certain general principles or concepts learned from research in animals may be transferred to the study of the human problem. Examples cited are concepts of communicable diseases; the discovery of viruses; the identification of mycoplasma infections; and recently the role of slow viruses in certain animal and human infections.

The current role of animal medicine in cancer research, prevention of cardiovascular diseases, and in congenital malformations are succinctly discussed.

The second lecture describes Animal Models of Human Diseases. The role of oncogenic viruses in animal cancers is a very concise review: in relationship to breast cancer; the herpes type virus as a cause of Marek's disease of chickens, lymphomas in certain primates, carcinomas of the cervix, and Burkitt's lymphoma. This is of great interest because of the ability to immunize chickens against Marek's disease, an economically important neoplastic disease of chickens. The renewed and expanded search for viral agents as part of the cause of certain collagen diseases was prompted by animal disease.

The relationship of alflatoxin ingestion to hepatic cancer in Africa was derived from the finding of disease in turkeys from peanuts contaminated by an alflatoxin producing fungus.

The third lecture, a comparative study of influenza, emphasizes the importance of transfer of virus between human and animal hosts. Antigenic drift in the influenza subtypes is discussed in relation to the peculiar epidemiology of influenza. The discussion of the natural occurrence of influenza in horses and in other animals is very interesting reading, and leads into the mutual dependence of the human and animal strains of influenza virus in developing new strains.

In the closing section on the origin of pandemics, Professor Beveridge anticipates some recent work of French scientists who have developed vaccines for influenza by predicting antigenic shifts in new epidemic strains.

These brief lectures contain a tremendous amount of worthwhile information presented in lucid and polished prose. The examples of disease in man and animals are well chosen and make for most interesting reading. Those of us who have urban roots and experience, whose animal contact has been in research laboratories or with domestic pets will find this book illuminating. We will close it with a sense of indebtedness to men whose observations of natural phenomenon have contributed not only to the animal kingdom but to better the lot of mankind.

JAMES A. CURTIN, M.D.

Current Research in Oncology. C. B. ANFINSEN, MICHAEL POTTER AND ALLAN N. SCHECTER, Editors. Price, $6.95. Pp. 214. New York: Academic Press, 1973.

A paperback publication which presents a series of lectures designed to review subjects in Biological Research for the scientists at the National Institutes of Health. A previous lecture series given in September 1971 has been published in a volume entitled, "Current Topics in Biochemistry." This group of lectures given in January 1972 was organized to provide an overview of broad fields of investigation in Oncology. The participants were selected for their eminence in their particular field of research in Oncology. The topics presented ranged from epidemiologic studies through basic biochemistry, virology, immunology, carcinogenesis and the current concepts and results of treatment with chemical agents. Each of the contributors presents a general survey of their area, integrating their own investigative endeavors into the presentation. There is an abundance of illustrative charts, tables and figures with each presentation. The sections on immunology and chemotherapy were of most interest to this reviewer. Each of the chapters presents an excellent insight to the current status of the field and the direction in which new progress can be anticipated. They also provide an excellent insight to the ever increasing interdependence of basic research in oncology to the clinical problems faced by the physician treating patients with cancer. As one reviews this material, one cannot help but be impressed with the extraordinary recent development of knowledge concerning the basic and clinical disciplines in oncology and the potential for the acceleration of the attack on the cancer, when further basic information is obtained and applied to the clinical aspects of human neoplasms. While not a publication that belongs on the shelves of every practicing physician, this book is a valuable adjunct to every library and to the physician responsible for the care of cancer patients.

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Charles C. Hageage, M.D.
1904–1973

Dr. Charles C. Hageage, Washington-area general practitioner, died September 2, 1973. He resided at 4000 Clagett Road, College Park, Maryland.

A native of Washington, D.C., he received his undergraduate and M.D. degrees from Georgetown University. He interned at Providence Hospital and Casualty Hospital in Washington, D.C., and served his residency in the United States Army. He served on the staff of Prince Georges General Hospital, Cheverly, Maryland, as an obstetrical assistant.

An Associate member of the Medical Society of the District of Columbia, Dr. Hageage was also a member of the Prince Georges County Medical Society, the Medical and Chirurgical Faculty of the State of Maryland and the American Medical Association.

He is survived by his wife, Sally Louise, of the home; a son, Dr. Hyoung Lee of New York; and two grandchildren.

Leonidas A. Ayton
1922–1973

Dr. Leonidas A. Ayton, specialist in Internal Medicine, died September 22, 1973. He resided at 7238 15th Place, N.W., Washington, D.C.

Born in Brooklyn, New York, he entered Howard University following graduation from high school, but left during World War II to enlist in the army. His service included duty on Okinawa and he was awarded the American Service Medal, the Asiatic Pacific Service Medal, the Good Conduct Medal and the World War II Victory Medal.

Upon returning to the states, he resumed his education at Howard University where he earned a Bachelor's degree and a Medical degree. He served his internship and residency at Freedman's Hospital in Washington, D.C.

Dr. Ayton received specialty training in internal medicine at Howard University College of Medicine and completed a fellowship in radiology at the National Institutes of Health.

Dr. Ayton was on the faculty of the Howard University College of Medicine and Freedmen's Hospital emergency care unit. He was also on the staff of D.C. General Hospital. From 1970 on, he was director of employee health at Howard University.

Dr. Ayton was an Active member of the Medical Society of the District of Columbia for twelve years.

He is survived by his wife, Mauree, and a daughter, Joy, both of the home; two brothers, Nigel, of Charlotte, N.C., and Eugene, of Philadelphia, Pa.; a sister, Ann A. White; and his mother, Edna W. Ayton, both of Atlantic City.

THE VIEW BOX

(from page 602)

DIAGNOSIS: **Retrocaval Ureter**

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Edited by Gunther J. Augustin, M.D.
Senior Attending Radiologist, Washington
Hospital Center, Washington, D.C.

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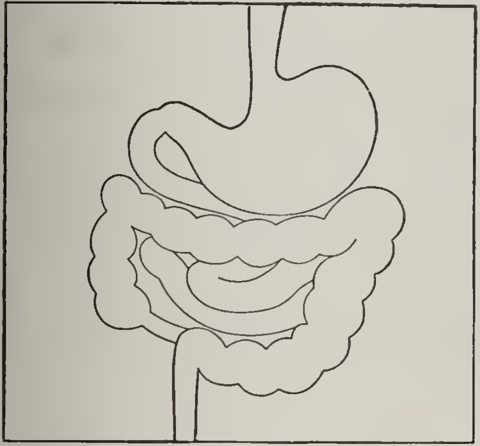
in "Gasspastic" conditions



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can do more

Contraindications: Anticholinergics should not be used in patients with glaucoma, known prostatic hypertrophy, or pyloric obstruction. Urinary retention may indicate the presence of prostatic hypertrophy. If it occurs, the dose should be reduced or the drug withdrawn. Also contraindicated in patients with known hypersensitivity to one of the components.
Side Effects: Dryness of the mouth, blurred vision, dysuria, skin rash, constipation or drowsiness may occur.

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Recommendations[†] on Combination Live Virus Vaccines

American Academy of Pediatrics

Committee on Infectious Diseases

In the September 15, 1971 *AAP Newsletter* sent to Academy members, the Committee on Infectious Diseases of the American Academy of Pediatrics stated its recommendations on the use of combination live virus vaccines. After a careful review of available data, the committee concluded that:

- "This information indicates that the products are both safe and effective when used as directed."
- The vaccine "...can, therefore, be recommended with the obvious advantages of reduction in the number of injections for any given child and a concomitant decrease in the required visits to a physician's office or clinic."

United States Public Health Service

Advisory Committee on Immunization Practices

In the April 24, 1971 issue of *Morbidity and Mortality Weekly Report,* the Advisory Committee on Immunization Practices of the United States Public Health Service presented recommendations on the use of combination live virus vaccines. The committee stated that:

- "Data indicate that antibody response to each component of these combination vaccines is comparable with antibody response to the individual vaccines given separately.
- "There is no evidence that adverse reactions to the combined products occur more frequently or are more severe than known reactions to the individual vaccines (see pertinent ACIP recommendations).
- "The obvious convenience of giving already selected antigens in combined form should encourage consideration of using these products when appropriate."

[†] For complete text of both recommendations see your MSD representative or write to Professional Service Dept., Merck Sharp & Dohme, West Point, Pa. 19486.

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MSD suggested immunization schedule for well babies

Age	**Vaccine(s)**
2 months	DPT (diphtheria-pertussis-tetanus) Oral poliomyelitis vaccine (triple)
3 months	DPT[1]
4 months	DPT Oral poliomyelitis vaccine (triple)
6 months	Oral poliomyelitis vaccine (triple)
12 MONTHS	**M-M-R (MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE, MSD)**

[1] This vaccination may be given at 3 months, 5 months, or at 6 months, depending on your preference or on the condition of the child.

Since vaccination with a live virus vaccine may depress the results of a tuberculin test for four weeks or longer, the test and the vaccine should not be given during the same office visit.

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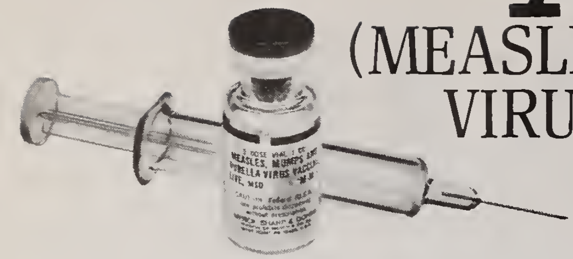
For a brief summary of prescribing information, please see following page.



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Contraindications: Pregnancy or possibility of pregnancy within three months following vaccination; infants less than one year old; sensitivity to chicken or duck, chicken or duck eggs or feathers, or neomycin; any febrile respiratory illness or other active febrile infection; active untreated tuberculosis; therapy with ACTH, corticosteroids, irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; gamma globulin deficiency, i.e., agammaglobulinemia, hypogammaglobulinemia, and dysgammaglobulinemia.

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other live virus vaccines, with the exception of monovalent or trivalent poliovirus vaccine, live, oral, which may be administered simultaneously; vaccination should be deferred for at least three months following blood transfusions or administration of more than 0.02 ml immune serum globulin (human) per pound of body weight, or human plasma.

Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination.

Excretion of the live attenuated rubella virus from the throat has occurred in the majority of susceptible individuals administered the rubella vaccine. There is no definitive evidence to indicate that such virus is contagious to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk.

Attenuated live virus measles, mumps, and rubella vaccines, given separately, may temporarily depress tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be scheduled before vaccination, to avoid the possibility of a false negative response.

Before reconstitution, refrigerate vaccine at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccine. If not used immediately, return reconstituted vaccine to refrigerator at 2–8 C (35.6–46.4 F), and discard after eight hours.

Adverse Reactions: To date, clinical evaluation has not revealed any adverse reactions peculiar to the combination. The adverse reactions that occurred were limited to those that have been reported previously for the component vaccines.

Fever, rash; mild local reactions such as erythema, induration, tenderness, regional lymphadenopathy; parotitis; thrombocytopenia and purpura; allergic reactions such as urticaria; arthritis, arthralgia, and polyneuritis.

Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions.

Encephalitis and other nervous system reactions that have occurred very rarely with the individual vaccines may also occur with the combined vaccine. Experience from more than 44 million doses of all live measles vaccines given in the U.S. by mid-1971 indicates that significant central nervous system reactions such as encephalitis, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered. A survey conducted in New Jersey in 1965 showed that 2.8 cases of encephalitis (of unknown cause) occurred per million children, ages 1–9 years per 30-day period." However, the Center for Disease Control has analyzed the reported reactions following measles vaccines and pointed out that "the clustering of cases in the period 6 through 13 days after inoculation as well as the recovery of measles virus (probably the vaccine strain) from the CSF of one patient does suggest that some of these cases may have been caused by the vaccine." The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis with measles (one per thousand reported cases).

Transient arthritis, arthralgia, and polyneuritis are features of natural rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. Such reactions have been reported with live attenuated rubella virus vaccines. Symptoms relating to joints (pain, swelling, stiffness, etc.) and to peripheral nerves (pain, numbness, tingling, etc.) occurring within approximately two months after immunization should be considered as possibly vaccine related. Symptoms have generally been mild and of no more than three days' duration. The incidence in prepubertal children would appear to be less than 1% for reactions that would interfere with normal activity or necessitate medical attention.

How Supplied: Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin, with a disposable syringe containing diluent and fitted with a 25-gauge, ⅝″ needle. Also in boxes of 10 single-dose vials nested in a pop-out tray with a separate box of 10 diluent-containing syringes.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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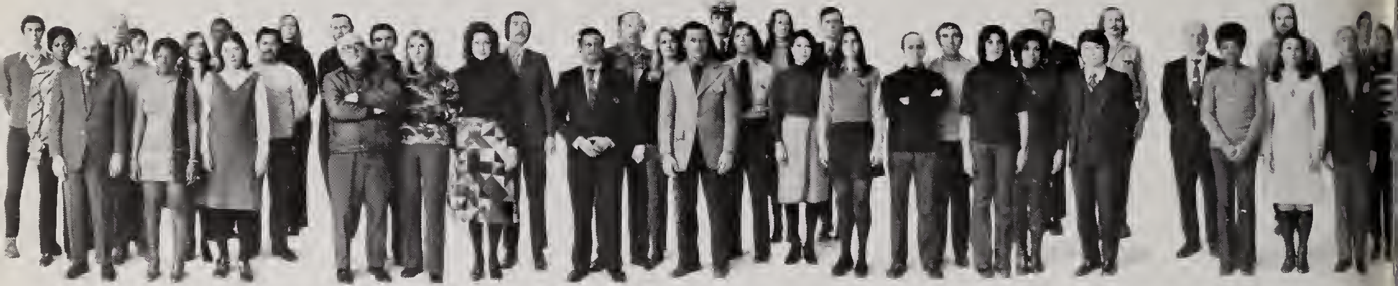

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Before deciding to make Valium (diazepam) part of your treatment plan, check on whether or not the patient is presently taking drugs and, if so, what his response has been. Along with the medical and social history, this information can help you determine initial dosage, the possibility of side effects and the ultimate prospects of success or failure.

While Valium can be a most helpful adjunct to your counseling, it should be prescribed only as long as excessive psychic tension persists and should be discontinued when you decide it has accomplished its therapeutic task. In general, when dosage guidelines are followed, Valium is well tolerated (see Dosage). For convenience it is available in 2-mg, 5-mg and 10-mg tablets.

Drowsiness, fatigue and ataxia have been the most commonly reported side effects.

Until response is determined, patients receiving Valium should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as driving or operating machinery.

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Nutley, N J. 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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The title should not exceed 80 characters and spaces. If a subtitle is used, it should not be connected grammatically to the main title.

The by-line, the author's given name and initial or given name alone should be supplied. The M.D. degree or highest academic degree should be listed for each author. Not more than six names should be included as authors, unless the communication is the report of a committee.

The footnotes, hospital and university affiliation when study was done, should be listed. Present affiliation and location (if different from that at time of study) should be given. Acknowledgements should be limited to persons, foundations, agencies or companies supplying drugs, funds or apparatus free of charge or otherwise making an extensive contribution to the study.

REFERENCES

The number of references should not exceed 18 single complete bibliographic citations, except in Special Articles.

References should be double spaced, on a separate sheet, and listed in order of citation in the text. Superior numbers should be inserted in the text at points of citation.

References should be given in the style regularly used in THE ANNALS, eg:

> Seremetis, M.D., DeGuzman, V.C., Lyons, W.S., Peabody, J.W.: Complications of Cardiac Pacemakers, Medical Annals of D.C., 1973, 42, 165.

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Use generic or descriptive names of drugs when available. Trade names, capitalized, may be given in parentheses when the drug is first mentioned.

Statistics should be checked for consistency within the text and for agreement with graphs or tables.

Laboratory data should not be given in abbreviated form but in full (e.g., "hemoglobin level, 12 Gm. per 100 ml." rather than "Hb. 12 GM.%).

Figures should be used for number 10 and above, laboratory measurements, percentages, and ages.

Metric equivalents should be given for dosage and body height and weight.

Centigrade equivalents should be given for Fahrenheit body temperatures, and vice versa.

Abbreviations should be used sparingly, with expansion given for those not listed in standard medical dictionaries.

The meaning of "we" should be clarified, especially if there is only one author. Avoid use of editorial "we."

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The summary should be brief, giving specific facts concerning the study and its results.

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The street address of one author should be given at the end of the article for reprint requests and correspondence.

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The title should be given at top of the page for each table.

Approximate placing of tables in text should be indicated, and each table should be referred to in the text.

The meaning of abbreviations should be clear, with those not listed in standard medical dictionaries expanded in a footnote to the table.

There should be no discrepancies in the totals.

Figures should be consistent with the text, without extensive duplication between tables and text or graphs.

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The top of each illustration should be indicated.

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Arrows should be inserted to pinpoint lesion or any important feature.

Do not attach paper clips or cellophane tape to photographs.

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The Upjohn Company 6

Pharmacy
Peoples Drug Stores 19

Sanitarium
Kalorama Convalescent Home, Inc. 22

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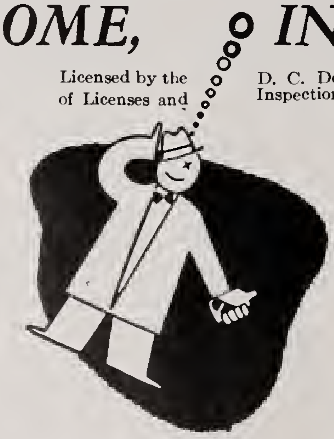

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulatio and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea an constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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